MEDICAL LIBRARY NOV 2 1949

BRITISH MEDICAL JOURNAL

JOURNAL OF THE BRITISH MEDICAL ASSOCIATION

SATURDAY OCTOBER 15 1949

TABLE OF CONTENTS

Malaria.—I N. HAMILTON FAIRLEY, C.B.E., M.D., F.R.C.P., F.R.S. 825

Clinical Value of Pregnanediol Assays G. I. M. SWYER, D.M., D.Phil., M.R.C.P. 830

Vesico-bullous Diseases Affecting the Eye ALICE CARLETON, M.D. 835

Retinal Arterial Occlusion in Migraine G. S. GRAVESON, M.D., M.R.C.P. 838

Studies in Primary Pleurisy with Effusion BRIAN C. THOMPSON, M.D. 841

Aetiology of Erythema Nodosum in Children S. A. DOXIADIS, M.D. 844

Post-operative Thrombosis G. W. VAUSE GREIG, M.B., F.R.C.S. 845

Incidence of Signs Usually Connected with Thyrotoxicosis W. P. U. JACKSON, M.D., M.R.C.P., D.C.H. 847

Actinomycotic Empyema HAROLD W. BOWYER, M.D. 848

MEDICAL MEMORANDA

Unusual Case of Nutritional Anaemia. M. MCLEAN, M.B., Ch.B., D.C.H. 849

An Extrarenal Hypernephroma. FRANK FORTY, F.R.C.S. 850

GENERAL ARTICLES AND NEWS

The Acute Throat. T. ANDERSON, M.D., F.R.F.P.S., F.R.C.P.Ed. 860

The Falkland Islands Dependencies Survey. J. M. ROBERTS, M.B., B.Chir. 863

THE PRISON POPULATION 864

AMINO-ACIDS AND PROTEIN HYDROLYSATES 865

JUVENILE DELINQUENCY 866

MEDICAL PROTECTION SOCIETY 867

NEW HUNTER DOCUMENTS EXHIBITED 868

A Modified Waters Apparatus for Thoracic Surgery. W. B. BACON, M.B., D.A. 868

MEDICO-LEGAL 881

UNIVERSITIES AND COLLEGES 881

MEDICAL NEWS 883

BIRTHS, MARRIAGES, AND DEATHS 885

QUESTIONS AND COMMENTS 885

REVIEWS

Neurohistology 851

Pulmonary Neoplasms 851

Operative Surgery 851

The Thyroid 852

Common-sense Psychiatry 852

Spanish Haematology 852

OBITUARY

Major Greenwood, D.Sc., F.R.C.P., F.R.S. 877

August Krogh, Ph.D. 879

Robert Milne, M.D., M.S., F.R.C.S. 879

W. G. S. Thomson, M.B., D.P.M. 880

Harry Freeman, F.R.C.S. 880

Donald Campbell, M.R.C.P. 881

Janet Y. Laidlaw, M.B. 881

LEADING ARTICLES

World Medical Association 854

Mr. Bevan's Review of N.H.S. 855

Pregnanediol Assays 856

ANNOTATIONS

Changes in Use of Hospitals 857

Parenteral Feeding 858

Erythema Nodosum and Nodal Erythema 858

Beginning Medicine 859

Refresher Course for General Practitioners 859

CORRESPONDENCE

Tuberculosis: Certain Unexplained Mortality Figures. IAN SUTHERLAND, D.Phil. 869

Modern Trends in Radiology. P. J. KERLEY, M.D.; A. GORDON EVANS, M.R.C.S.; F. KELLERMAN, M.D. 870

Essential Hypertension in Pregnancy. J. TRUETA, M.D 871

A New Neonatal Syndrome. F. P. HUDSON, M.R.C.P.Ed., and ANNE MCCANDLESS, M.D. 871

SUPPLEMENT

The Secretary Reports *165*

The First Year *166*

Health Service.—N.H.S. IN SCOTLAND—CHANGES IN THE USE OF HOSPITALS—SPECIMENS IN THE POST—VARIATION IN CAPITATION FEES—ENTRY INTO PRACTICE—DOMICILIARY CONSULTATION *168*

HEARD AT HEADQUARTERS *170*

QUESTIONS ANSWERED *170*

AUSTRALIAN HEALTH SERVICE *170*

ANNUAL CONFERENCE OF REPRESENTATIVES OF LOCAL MEDICAL COMMITTEES *170*

CORRESPONDENCE *172*

THE MEDICAL ASSOCIATION OF EIRE *173*

ASSOCIATION NOTICES *174*

CORRESPONDENCE—*cont.*

Penicillin in Early Syphilis. A. O. FERGUSSON ROSS, M.D. 871

Myxoedematous Madness. C. A. H. WATTS, M.D.; MARTIN ROTH, M.D. 871

Old Age. J. RUSHWORTH LUND, M.R.C.S.; EILEEN M. HICKEY, M.D., M.P. 872

B.M.A. Tuberculosis Group. S. G. TIPPETT, M.B. 872

Men, Machines, and Materialism. R. SESSIONS HODGE, M.R.C.S. 872

St. Luke's Day. HERBERT CAIGER, F.R.C.S. 873

Sensitivity to Streptomycin. N. W. HORNE, M.B. 873

Massage with Adrenaline. LOUIS MOSS, M.R.C.S. 874

Simulated Amnesia. W. A. O'CONNOR, L.M.S.S.A. 874

Hypnosis in Treatment. K. M. HAY, M.B. 874

Treatment of Early Pulmonary Tuberculosis. J. HERBERT-BURNS, M.B. 874

Manipulation for Low Backache. TREVAN HAMBLY, M.R.C.S. 874

Locked Twins. JAMES W. DAVIDSON, M.B. 875

Treatment of Cutaneous Anthrax. L. HOYLE, M.B. 875

Treatment of Ringworm of the Scalp. A. J. E. BARLOW, M.D., F. W. CHATTAWAY, Ph.D., and C. S. WHEWELL, Ph.D. 875

University Degrees. E. O'C. TANDY 875

Cigarette Cough. B. J. GALLIGHAN, M.B. 876

Diabetes and Gout. R. TRUSCOE, Ph.D. 876

Dysentery in Monkeys. R. E. REWELL, M.D., and R. F. BRIDGES, B.M. 876

Points from Letters 876

Epidemiology Section 882

BRITISH MEDICAL ASSOCIATION, TAVISTOCK SQUARE, LONDON, W.C.1

No. 4632, WEEKLY, PRICE 1/6

Copyright

REGISTERED AS A NEWSPAPER

When the instep steps out

Buying children's shoes too big "to allow for growth" usually means that the shoe round instep and heel is too loose. The foot slips forward and the toes get almost as cramped as they would if the shoes were too small.
To prevent this, Clarks make their children's shoes to fit snugly round the upper part of the foot while leaving space for growth at the toe.
Each size and half-size is made in several widths and girths, and Clarks' Footgauge determines which is each child's own particular size *and* shape. Feet shod with such care will always remain well-formed.

Clarks

Children's shoes are made to fit

C. & J. CLARK LTD., STREET, SOMERSET

The **MAGILL** FOLDING LARYNGOSCOPE

With 3 Interchangeable Blades.

(The largest may be used with a No. 10 Magill Cuffed Tube.)

Stainless steel blade ensures long life and avoids danger of patient inhaling a flake of plating.

Reliable electrical system. No obstruction to manipulation of endotracheal tubes.

An exclusive M.I.E. design

Now available from stock

Macintosh Curved Blade to fit same handle also available.

MEDICAL & INDUSTRIAL EQUIPMENT LTD.
SPECIALISTS IN ANÆSTHETIC APPARATUS
12, New Cavendish Street, London, W.1.
Telephone: WELbeck 1851 & 1504

As an Antacid
or in febrile conditions
Invalid
Lembar
justifies the doctor's highest recommendation. Available in limited quantities

Lemon Juice	38.0% w/v
Sucrose	23.7% w/v
Liquid Glucose B.P.	28% w/v (*equivalent to Dextrose (Monohydrate)* 10.5% w/v)
Barley (*Sol. Extract*) from 7.4% w/v	

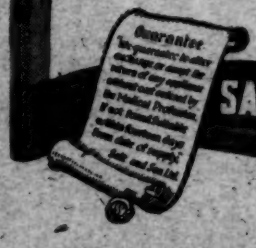
Plus flavouring and permitted preservative.

MADE BY RAYNER AND COMPANY LIMITED, LONDON, N.18

HIGHLY SATISFACTORY RESULTS
follow the adoption of
SALT'S PATENT COLOSTOMY BELT

Since we first introduced this Belt we have supplied many hundreds, and the results have been highly satisfactory. Outstanding advantages are: (1) Receiver is detachable and sterilizable by boiling; (2) Bag easily removed without removal of belt; (3) Bag easily emptied and washed; (4) No crevices or metal fittings to hold faeces; (5) Smell reduced to a minimum; (6) Less bulk than the old style. Bags are easily and economically replaced. Further details and Measure/Order forms available to professional people on request.

Appointments at London address: 1, STANLEY HOUSE, 103, Marylebone High Street, London, W.1. Tel.: Welbeck 3034.



SALT & SON LTD · BIRMINGHAM 2

BRITISH MEDICAL JOURNAL

LONDON SATURDAY OCTOBER 15 1949

MALARIA

WITH SPECIAL REFERENCE TO CERTAIN EXPERIMENTAL, CLINICAL, AND CHEMOTHERAPEUTIC INVESTIGATIONS*

BY

N. HAMILTON FAIRLEY, C.B.E., M.D., D.Sc., F.R.C.P., F.R.S.

Wellcome Professor of Tropical Medicine, London School of Hygiene and Tropical Medicine; Physician, Hospital for Tropical Diseases, University College Hospital, London

LECTURE I: THE LIFE CYCLE

Under the stimulus of war in the Tropics, more scientific effort and medical man-power were directed to intensive study and research on malaria than to any other disease in history. In such circumstances it is hardly surprising that great advances in our knowledge of this disease and of its control have resulted during the past decade.

The discovery of insecticides like D.D.T. and "gammexane" is now leading to the control of mosquito-breeding and the destruction of adult mosquitoes on a scale which is revolutionary. Similarly, the synthesis of new antimalarial drugs in the U.K. and the U.S.A. proceeded on a scale that far surpassed all previous achievements and brought the control of malaria by chemotherapeutic means within the range of practical possibility. In connexion with the discovery of proguanil (paludrine) by Curd, Davey, and Rose (1945) over 1,000 new compounds were produced and tested against bird malaria. In the United States over 14,000 new compounds were screened for their therapeutic action in bird malaria, and over 100 of these were subsequently tested on man. The most promising of the antimalarial drugs synthesized in U.S.A. and U.K., such as certain sulphonamides, mepacrine, "sontochin," "chloroquine," and proguanil, were tested for suppressive and prophylactic action on experimentally infected volunteers living under tropical conditions by Australian medical research units established near Cairns, in Northern Queensland.

The discovery made by Shortt and his colleagues last year of the pre-erythrocytic and exo-erythrocytic cycle in monkey malaria (*Plasmodium cynomolgi*) and of pre-erythrocytic schizonts in benign tertian malaria in man was long overdue, establishing as it did the tissue phase in mammalian malaria some fifteen years after its demonstration in avian malaria. It was a discovery of outstanding importance not only from the parasitological point of view but also because of its clinical and chemotherapeutic implications. This first lecture will be devoted to this subject.

*First of the Croonian Lectures delivered at the Royal College of Physicians of London on May 3 and 5, 1949.

Erythrocytic and Sporogonous Cycle

At the beginning of the present century the life cycle of the malaria parasite appeared to be completely known. A schizogonous cycle in the red cells which accounted for clinical attacks and a sporogonous cycle in the mosquito had been firmly established. It is true Grassi (1900) had considered there might be another developmental cycle in man during the incubation period, but after Schaudinn (1902) vividly described just how the sporozoites actively penetrated the red cells the chain of events in the life cycle appeared complete. The whole question was reopened some thirty years later mainly because it was not possible to explain the behaviour of antimalarial drugs like quinine and "plasmoquine" (pamaquin) on this basis.

Sergent and Sergent (1922) had noted that though quinine destroyed malaria parasites once they appeared in the blood it exerted no therapeutic action when given during the incubation period. Yorke and Macfie (1924) next reported that quinine given during the incubation period resulted in radical cure of benign tertian malaria which had been transmitted by blood inoculation (trophozoite-transmission), whereas it merely prolonged the incubation period slightly when the disease was transmitted by infective mosquitoes (sporozoite-transmission).

In a paper read before the Royal Society of Tropical Medicine and Hygiene in January, 1931, James (1931a) confirmed these observations and discussed several views which had been put forward to explain the different therapeutic response induced by quinine in patients infected by blood inoculation and those infected by mosquitoes. One theory was that some of the sporozoites, instead of entering the red blood corpuscles, entered connective-tissue cells or the cells lining the capillary blood vessels; another theory was that the sporozoites actually penetrated into the interior of the red cell, whereas merozoites merely attached themselves to the outside of the corpuscle. James favoured the latter view and considered that Schaudinn's account of the penetration of the corpuscle by the sporozoite was "so clear-cut and detailed as to admit

of no question." In the discussion which followed, Warrington Yorke (1931) was frankly sceptical, stating that he had spent some weeks trying to repeat Schaudinn's observations without success.

In August of the same year, James, Nicol, and Shute (1931) reported the prevention of mosquito-transmitted benign tertian malaria in volunteers by the use of pamaquin: 20 mg. was given on the day before infection, and 60 mg. for the next six days. James (1931b) considered that these findings regarding pamaquin favoured the conception that the malaria parasites passed through a tissue stage and, in a communication read by Schüffner at Amsterdam in December, suggested that the time had come "to consider whether knowledge concerning the life cycle of the malaria parasite was complete or not." He pointed out that Schaudinn's observations had never been confirmed, that sporozoites were essentially parasites of tissue cells, and suggested that possibly, on entering the blood, they were carried to reticulo-endothelial cells of the lungs and other organs, where they underwent "a cycle of growth or sporulation similar to the cycle of the allied bird parasite, *Halteridium*."

Tissue-phase Parasites in Avian Malaria

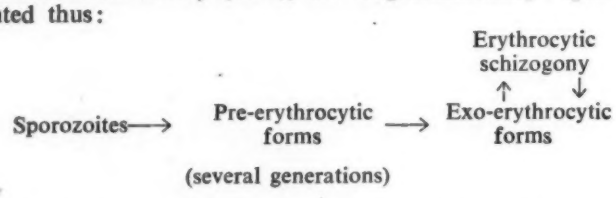
The hypothesis that there was a tissue phase of the parasite soon received support from the discoveries made in bird malaria, but it took another ten years' intensive experimental work to complete the story.

Garnham (1948), in his excellent review on this subject, regards Raffaele (1934, 1936) as probably being the first investigator to recognize the significance of exo-erythrocytic parasites in bird malaria, though undoubtedly many observers had seen them much earlier. The important publications of Huff and Bloom (1935), Brumpt (1937), and James and Tate (1937, 1938) followed shortly after those of Raffaele.

Two distinct schizogonous cycles have been recognized in the tissues: (1) the pre-erythrocytic, which occurs during the incubation period before asexual parasites appear in red blood corpuscles; and (2) the exo-erythrocytic schizogony, which is found after parasites have gained access to the corpuscles and persists in the late stages of the infection.

In seven species of plasmodia producing malaria in birds, Porter (1942) differentiated between two types of exo-erythrocytic schizogony—one occurring in *P. gallinaceum* and the other in *P. elongatum* infections. Schizogony of gallinaceum type occurred mainly in the reticulo-endothelial system, that of elongatum type was confined to the wandering cells of the blood and haemopoietic organs.

The salient features in the tissue cycle in avian malaria, modified from Davey (1944), are diagrammatically represented thus:



1. *Pre-erythrocytic Schizogony.*—The pre-erythrocytic forms in *P. gallinaceum* were first discovered by Mudrow (1940) and Shortt, Menyon, and Iyer (1940). A few years later Huff and Coulston (1944) injected enormous numbers of sporozoites into localized skin areas in chicks, demonstrating that sporozoites penetrated the reticulo-endothelial cells of the skin in from half an hour to six hours and underwent a schizogonous cycle lasting 42 hours. Primary forms also developed in the spleen and other organs intercurrently. When the schizont ruptured, the first-generation merozoites (cryptozoites) penetrated adjacent reticulo-endothelial cells, where they underwent one or more schizogonous cycles before liberating second- or third-generation merozoites (metacryptozoites) into the blood. By the fifth day Reichenow and Mudrow (1943) distinguished two types of schizonts—the macroschizonts containing 100–200 macromerozoites which are destined to invade fresh reticulo-endothelial cells, and the microschizonts containing up to 1,000 micromerozoites which invade the red blood corpuscles. Sub-inoculations with saline suspension of organs containing pre-erythrocytic parasites consistently yield positive results in avian malaria.

2. *Exo-erythrocytic Schizogony.*—Little difference has been observed between the pre-erythrocytic and the later exo-erythrocytic schizonts; pigment is absent from both, since they develop in cells containing no haemoglobin. The distribution of exo-erythrocytic schizonts in the organs has been described by several different workers. James and Tate (1937, 1938), who independently described the schizogonous cycle in the reticulo-endothelial cells and monocytes of fowls infected with *P. gallinaceum*, first suggested that the non-committal title "exo-erythrocytic" be used to differentiate it from erythrocytic schizogony. They found that the brain, liver, lungs, and spleen were important sites for the tissue stages, and that, even after the erythrocytic parasites had disappeared from the blood with quinine treatment, birds died from blockage of the vessels of the brain resulting from schizonts developing in the reticulo-endothelial lining.

Coulston and Manwell (1941) actually produced experimental infections with *P. circumflexum* by the injection of a single parasitized corpuscle, and after several passages exo-erythrocytic forms appeared. After intravenous inoculation of blood containing *P. gallinaceum*, Tullis (1947) found that small numbers of exo-erythrocytic schizonts appeared on the fourth day in reticulo-endothelial cells of the spleen and on the sixth day in the liver, heart, lungs, and intestine. Thus in bird malaria tissue schizonts may originate directly from pre-erythrocytic parasites or indirectly from the blood parasites.

Tissue-phase Parasites in Monkey Malaria

In monkeys, malaria which is caused by *P. cynomolgi* is readily transmitted experimentally by *Anopheles maculipennis atroparvus*. Other well-known simian parasites, like *P. knowlesi* and *P. brazilianum*, are unfortunately unsuitable for studying tissue forms, since the mosquito vector is unknown.

In *P. cynomolgi* infections the erythrocytic parasites closely resemble vivax parasites morphologically and appear in the blood about the ninth day. Relapses are common up to six to eight months, when spontaneous cure generally occurs. Coatney and Cooper (1948) report that pentaquine and pamaquin with or without quinine bring about radical cure. The disease closely resembles benign tertian malaria in man, especially the New Guinea and Chisson strains characterized by short-term relapses. Much intensive research work has been undertaken in America, India, England, and other parts of the world during the past decade in an effort to demonstrate tissue forms in monkeys infected with this species of plasmodium. It was not until last year, however, that Shortt, Garnham, and Malamos (1948), at the London School of Hygiene and Tropical Medicine, discovered pre-erythrocytic forms in the liver of a monkey (*Macaca mulatta*) intensely infected with sporozoites seven days previously.

1. *Pre-erythrocytic Parasites.*—In this experiment over 500 hyperinfected mosquitoes (*A. maculipennis atroparvus*) were

first fed on this monkey; then the entire batch was ground up with heparinized plasma and injected parenterally. The pre-erythrocytic forms were confined to the parenchyma cells of the liver, sections of which showed ovoid blue areas, averaging about 26 μ in diameter, composed of plasmodial masses containing chromatin particles. Later work showed that mature schizonts on the eighth or ninth day contained nearly 1,000 merozoites; each merozoite measured a little over 1 μ in diameter and was composed of a mass of cytoplasm with a small fragment of chromatin on one side. When the schizont ruptured, the merozoites escaped into the circulation via the hepatic sinusoids, and invasion of the residual mass by lymphomacrophage cells, plasma cells, and polymorphonuclear cells occurred. Pre-erythrocytic schizogony in *P. cynomolgi* was later confirmed by Hawking, Perry, and Thurston (1948).

2. *Exo-erythrocytic Forms.*—Some months later Shortt and Garnham (1948) demonstrated the late tissue stages (exo-erythrocytic schizonts) in the parenchyma cells of the liver of a monkey which had been hyperinfected 103 days previously; by this time the disease was latent and parasites had temporarily disappeared from the peripheral blood. The late exo-erythrocytic forms resembled the pre-erythrocytic forms in most respects, a possible difference being the presence of a limiting membrane surrounding the younger schizonts. These exo-erythrocytic forms undoubtedly represent the relapse forms. Shortt and Garnham (1948) consider that exo-erythrocytic schizogony is maintained throughout the whole course of the disease, and that the cellulo-humoral antiparasitic defence mechanism of the host is operative only against the erythrocytic parasites, resulting in the destruction of merozoites entering the circulating blood. This immunity mechanism, which comes into play exclusively against the erythrocytic parasite, is not active against the exo-erythrocytic forms themselves, possibly because of their intracellular habitat. Those merozoites destined to invade other liver cells are similarly protected, so that the exo-erythrocytic cycle can go on indefinitely quite independently of blood infection.

Comment.—The success attained by Shortt and his colleagues, where so many others had failed, was no doubt due to the intense hyperinfection adopted and the improved technique devised for staining tissue parasites. In the monkey it involved the introduction of hundreds of thousands of sporozoites by mosquito-bite and by inoculation either of a whole mosquito intraperitoneally or of the salivary glands intravenously (Garnham, 1948). Investigators had also been misled to some extent because the tissue phase in mammalian malaria differed in certain unexpected ways from avian malaria. Thus in monkey malaria schizogonous development takes place in the parenchymatous cells of the liver, not in reticulo-endothelium, while subinoculation with saline suspensions of the liver into clean monkeys invariably yields negative results, probably because there is only one generation of pre-erythrocytic schizonts whereas in avian malaria there are several.

TISSUE-PHASE PARASITES IN HUMAN MALARIA

A. Benign Tertian Malaria

Pre-erythrocytic Phase.—Shortt, Garnham, Covell, and Shute (1948) also reported the pre-erythrocytic stage of *P. vivax* in a volunteer patient who had been exposed to heavy biting by infected mosquitoes (*A. maculipennis atroparvus*) and had in addition received an intravenous injection of sporozoites derived from their salivary glands. Laparatomy and liver biopsy were performed seven days later under local analgesia. Sections revealed plasmodial masses in the parenchyma cells, measuring up to 42 μ in diameter, which were studded with chromatin particles and some of which contained vacuoles. In appearance they closely resembled the pre-erythrocytic schizonts found in *P. cynomolgi* in monkeys.

From subinoculation experiments undertaken by Fairley (1945) and Fairley *et al.* (1947) it is evident that vivax sporozoites after being inoculated by mosquitoes rapidly gain access to the blood but soon again leave the circulation, invading the parenchyma cells of the liver, as shown by Shortt and his colleagues. Here they pass through a prolonged developmental cycle lasting at least eight days. The mature schizonts rupture and merozoites enter the circulation with great regularity on the ninth day of infection, producing a subpatent parasitaemia which may last another one to seven days. In thick films scanty parasites—i.e., to the order of 1 per c.mm.—appear on an average 12 days after exposure (range 10–15 days). This at least is the chain of events so far as the New Guinea strain of *P. vivax* is concerned.

Exo-erythrocytic Forms.—There is so much indirect clinical evidence supporting the presence of persistent exo-erythrocytic forms in benign tertian malaria, and vivax infection with short-term relapses is so similar to cynomolgi malaria, that for all practical purposes their existence can be accepted. Latency and the tendency to multiple relapses can best be explained on the basis of persisting exo-erythrocytic forms, while the different therapeutic response to various schizonticidal drugs like mepacrine, chloroquine, and quinine observed in blood-inoculated and mosquito-transmitted malaria is otherwise inexplicable. The schizonticidal drugs rapidly produce radical cure in trophozoite-transmitted vivax malaria. In sporozoite-transmitted malaria, though they rapidly produce clinical cure and clear the blood completely of parasites as revealed by negative subinoculations and negative blood smears, parasites later reappear and overt relapses follow. To establish radical cure during the overt attack one of the 8-amino-quinoline compounds like pamaquin or pentaquine is given in full dosage in combination with quinine. During the long latency characteristic of the St. Elizabeth strain of *P. vivax* radical cure has been reported by White *et al.* (1948) at a time when erythrocytic parasites are entirely absent from the blood: such a result can be due only to exclusive action on exo-erythrocytic forms.

Exo-erythrocytic Forms and Immunity Response.—According to Shortt and Garnham (1948) exo-erythrocytic schizogony is maintained throughout the whole course of the disease, and the antiparasitic defence mechanism of the host is directed essentially against the erythrocytic parasites, not against pre-erythrocytic or exo-erythrocytic forms. They suggest that latency and relapse in vivax malaria are governed by this immunity defence mechanism. Acquired antiparasitic immunity and tolerance result from a specific cellulo-humoral response to the invasion of the blood by erythrocytic parasites—provided that the parasitaemia is of sufficient duration and intensity to elicit an adequate response. The experimental studies of Taliaferro and Mulligan (1937) indicate that the spleen, liver, and bone marrow undergo considerable lymphoid hyperplasia with cytogenesis of macrophages, parasites being mainly destroyed locally in these organs. Immunity is paid for in terms of blood destruction, overworked sweat glands, and fever, but it is more easily acquired with some vivax strains than with others. Whether it is complete or partial will be determined by the trophozoite experience of the individual (total antigenic stimulus) and the strain of *P. vivax* implicated. With New Guinea strains solid immunity results in untreated patients only after prolonged primary fever, or if this be cut short by antimalarial

therapy it may arise later during febrile relapses in which treatment is withheld or markedly delayed.

Latency and Relapse

1. *Latency with Immunity.*—Blackburn (1948) was able to show that volunteers infected with the New Guinea strain of *P. vivax* who developed solid tolerance and antiparasitic immunity to their infections constantly had vivax trophozoites in the peripheral circulation, though their density rarely exceeded 1 per c.mm. over several months of observation. Gametocytes were never seen during the period of immunity, and mosquitoes fed on these subjects failed to become infected. The low densities of trophozoites caused no constitutional disturbances whatsoever. These volunteers had normal haemoglobin concentrations and red blood cell counts, their spleens were not palpable, and they were perfectly fit. Attempts to induce relapses by reinfection with the same strain of *P. vivax* (superinfection) were unsuccessful.

2. *Latency and Suppression with Mepacrine.*—In experimentally infected volunteers taking 0.1 g. of mepacrine daily for many months, Fairley and his colleagues (1945, 1947) found that vivax parasites were not demonstrable in thick smears, that subinoculations invariably became positive on the 9th day and were generally negative after the 14th day of infection. In one patient receiving 50 infective vivax bites on zero day, subinoculations with 20 ml. of blood were made at four-day intervals between the 9th and 142nd days while receiving suppressive mepacrine. Positive results were recorded on the 9th, 13th, and 42nd days after infection; the remaining 32 subinoculations were negative. Parasites were absent in blood films on the 42nd day, when the positive subinoculation occurred. Overt vivax malaria occurred on the 177th day, 35 days after mepacrine ceased. It is noteworthy that in heavy experimental infections the 42nd day is about the time the first relapse appears in patients whose primary fever has been treated with schizonticidal drugs. After stopping suppressive mepacrine overt vivax malaria occurred within three to ten weeks in 97% of cases. No evidence of immunity was observed in these patients: this is hardly surprising, as merozoites are destroyed shortly after reaching the blood with the New Guinea strain of *P. vivax*, provided the plasma mepacrine concentration is satisfactory.

When suppressive drug medication is stopped overt attacks occur in a few weeks with the ordinary New Guinea and the Chisson strain of *P. vivax*, which have a close relapse pattern, but with the St. Elizabeth, Madagascar, and local Dutch strains, which have had suppressive treatment during the first four weeks after infection, overt malaria does not appear until approximately nine months after the original infection.

3. *Latency and Long-term Relapse without Immunity.*—True latency with long-term relapse is encountered with certain strains of *P. vivax* both in natural infections and where the primary fever has been suppressed by antimalarial drugs or treated early in the febrile attack.

(*a*) *Latency Following Suppression of Primary Fever.*—Important experimental investigations in volunteer prisoners in the U.S.A. have recently been carried out with the St. Elizabeth strain of *P. vivax*. This strain produces an infection with a long latent period of eight to nine months between the early treated primary attack and the first relapse; thereafter a series of short-term attacks begin. White *et al.* (1948) report the complete absence of circulating parasites during this long latent phase; thick blood smears were always negative, and massive subinoculations with 250–300 ml. of blood to non-immune recipients failed to produce malaria. In addition Cooper *et al.* (1947) report that during this period the individual harbouring a latent infection is susceptible to superinfection with parasites of the same strain, indicating that no immunity has developed. Coatney and Cooper (1948) conclude that it is impossible to account for this long latent interval on the basis of immunity to erythrocytic parasites, and suggest that it may represent a period when the fixed-tissue reservoir is not casting erythrocytic invading forms into the circulation.

(*b*) *Natural Latency with Prolonged Incubation Period.*—This condition is well recognized in natural infections in Europe, where in the early spring primary attacks may be caused by infections contracted in the previous summer and autumn. James (1931a) reported that 12 patients at Horton did not develop overt vivax malaria until six to ten months after being bitten by infective mosquitoes (Madagascar strain). Swellengrebel and de Buck (1938) found that many of their patients infected with the local Dutch strain fell into this category, not developing overt malaria for some nine months after exposure to infective mosquitoes biting at any time of the year. There is a normal average incubation period of 21 days with this Dutch strain, and eight to nine months elapse between primary fever and the first relapse.

Shute (1946) produced good evidence that natural latency in vivax malaria—i.e., an overt attack in patients infected eight to nine months previously—was attributable to low sporozoite dosage; he suggested that relapses might be due to sporozoites which had been lying dormant in tissue cells, pointing out that they were able to survive for many months in the insect carrier. According to Shute, natural latency occurs only when the sporozoites injected are too few to set up an immediate attack: about 2,000 sporozoites were regarded as the minimum necessary to establish infection by intravenous injection.

Serial subinoculations have not been performed on and after the ninth day following infection in these latent cases, but it seems likely that owing to a paucity of inoculated sporozoites only scanty pre-erythrocytic schizonts are produced; the resulting erythrocytic merozoites are evidently so few that non-specific phagocytosis in the liver, spleen, bone marrow, and blood—i.e., natural immunity—suffices to prevent the establishment of an effective parasitaemia. In consequence primary fever fails to develop, and with the Madagascar and Dutch strains an overt attack is not encountered for eight to nine months.

Comment.—Results based on infections with the New Guinea strain of *P. vivax*, which has a short-relapse pattern, support the view that latency is related to, and controlled by, the immunity response of the host as in cynomolgi malaria in monkeys.

In vivax infections with the St. Elizabeth, the Madagascar, and the local Dutch strains, which are characterized by long-term latency before relapse, it is difficult to visualize how any immunity could have been acquired. In these circumstances the most likely explanation is a failure of erythrocytic merozoites to reach the blood stream and establish a parasitaemia, as Coatney and Cooper (1948) have pointed out. The failure to establish even a subpatent parasitaemia during this long-term latency is revealed by the negative results obtained with massive subinoculations in non-immunes. This might result from (1) cessation of exo-erythrocytic schizogony with the production of resting-stage parasites; (2) a slowing down of exo-erythrocytic schizogony and/or a decrease in the ratio of erythrocytic to liver-invading merozoites, so few of the former reaching the circulating blood that natural immunity suffices to prevent an effective parasitaemia developing; and (3) a switch-over to the exclusive production of liver-invading merozoites during exo-erythrocytic schizogony, the rate of which may or may not be retarded. It is suggested that No. 3 constitutes the most feasible working hypothesis, and that the atypical exo-erythrocytic schizogony which characterizes long-term latency is determined by the innate

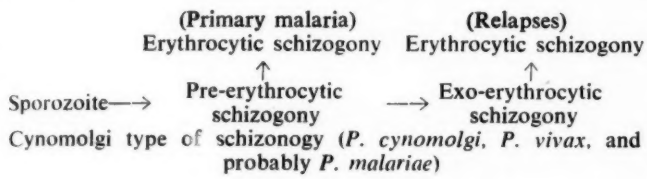
biological qualities of the vivax strains under consideration. Latency ends when there is a reversion to normal exo-erythrocytic schizogony, with the production of the usual ratio of erythrocytic to liver-invading merozoites.

Once overt malaria supervenes after this long latent period it is interesting to note that several relapses not infrequently follow at monthly periods (close relapse pattern), indicating that normal exo-erythrocytic schizogony has been established and is being maintained.

B. Quartan Malaria (P. malariae)

In quartan malaria both sporogonous and erythrocytic schizogonous cycles proceed very slowly. Nothing is known of the tissue cycle. Unfortunately, subinoculations have not been performed during the incubation period, so no assessment can be made of the probable duration of the pre-erythrocytic cycle. The long latent periods, the presence of late relapses, and the difficulty of attaining radical cure suggest that exo-erythrocytic schizogony persists for many years. Blood-transfusion accidents, in which quartan malaria is transmitted by a donor who has been away from malarious areas for many years and been completely free from clinical attacks during this period, also support this view.

The following diagram depicts the tissue phases of the malaria parasite in monkeys infected with *P. cynomolgi*. It is suggested that the term "cynomolgi type" could usefully be employed in mammalian malaria for this type of schizogony. There is abundant indirect evidence that *P. vivax* follows the cynomolgi type of schizogony, and it seems highly probable that *P. malariae* does likewise.



C. Malignant Tertian Malaria (P. falciparum)

The present position in regard to the tissue phase of *P. falciparum* is much the same as that of *P. vivax* last year, before pre-erythrocytic forms had been discovered.

Pre-erythrocytic Cycle.—Subinoculation experiments reported by Fairley (1945) and Fairley *et al.* (1947) have shown that when donors are bitten by from 7 to 24 infective mosquitoes at a single session lasting 5 to 15 minutes sporozoites may gain access to the circulation during the time of biting or be detected at intervals up to 60 minutes after cessation of biting. Thereafter subinoculation results were uniformly negative until the seventh day, when they again became consistently positive. All of 41 subinoculations with 500 ml. of blood made from volunteers infected 6½ to 8½ days previously were positive.

The only reasonable interpretation of these findings is that, in falciparum as in vivax malaria, sporozoites inoculated into the tissues by infective anophelines rapidly gain access to the circulating blood and subsequently disappear rapidly from the circulation. Presumably they enter the parenchyma cells of the liver, where they develop into pre-erythrocytic schizonts, which liberate mature merozoites into the blood with extraordinary regularity on the seventh day of infection.

The causal prophylactic action of proguanil in malignant tertian malaria also suggests the existence of early tissue forms which are many times more sensitive to the drug than either sporozoites or merozoites. Fairley *et al.* (1946) found that a single dose of 50 mg. given between the 39th and the 131st hour following exposure to biting afforded complete protection; parasites never appeared in the blood and overt malaria failed to develop. Eight out of 10 volunteers receiving as little as one single dose of 10 mg. between 48 and 120 hours after infection were completely protected. It was found that proguanil (0.3 g.) given about the time of exposure to infection generally failed to protect; malaria could be prevented with certainty only if 1 g. of the drug was given. The conclusion reached was that proguanil had no action on the sporozoites as such, its lethal effect being due to small quantities persisting in the circulation and acting on tissue forms early in the pre-erythrocytic cycle. Later on the seventh day, by which time merozoites were entering the circulation, a single dose of 0.3 g. failed to give protection, though it was effective up to 144 hours. The most reasonable explanation of these experimental findings is that proguanil has a highly selective action on the pre-erythrocytic forms in falciparum malaria.

Exo-erythrocytic Cycle.—Though indirect evidence favouring a pre-erythrocytic stage is entirely convincing in malignant tertian malaria, the same cannot be said in regard to the existence of later exo-erythrocytic forms. None of the evidence advanced as indicating a persistent phase in vivax malaria is forthcoming for falciparum malaria. Thus in falciparum malaria (1) long latent periods are absent and recrudescences occur separated by only two to three weeks of apyrexia; (2) once the blood has been completely cleared of falciparum parasites by schizonticidal drugs like quinine, mepacrine, or chloroquine radical cure has been achieved; (3) it is useless to resort to the 8-amino-quinolines for radical cure as in benign tertian malaria: drugs of this group, though they are effective in preventing malignant tertian malaria when they are given in full dosage during the first six days of infection, are quite ineffective in the treatment of the acute attack and the eradication of the infection; this is because they are very poor schizonticides for *P. falciparum*; and (4) sporozoite-transmitted malaria is just as rapidly and radically cured by schizonticidal drugs as is trophozoite-transmitted malaria; this is contrary to the findings in benign tertian malaria.

To explain these therapeutic results it would be necessary to assume that, while the hypothetical exo-erythrocytic forms in falciparum malaria are just as susceptible to schizonticidal drugs as are asexual erythrocytic parasites, they are insusceptible to the 8-amino-quinolines. This would be exactly the reverse of the action of these drugs in benign tertian malaria. In toxic dosage the 8-amino-quinolines are known to have a true causal prophylactic effect in malignant tertian malaria, where their action on pre-erythrocytic forms is much more potent than in vivax malaria. Why, then, should they have no effect on exo-erythrocytic forms in malignant tertian malaria while destroying the exo-erythrocytic forms in benign tertian malaria?

All available data indicate that in malignant tertian malaria, after the pre-erythrocytic schizonts have ruptured and discharged their merozoites into the circulation on the seventh, and possibly the eighth and ninth days as well, the pre-erythrocytic schizonts disappear entirely without giving rise to later exo-erythrocytic forms. The subsequent course of the disease will thus be determined solely by erythrocytic schizogony, and if the parasitaemia be eradicated radical cure results.

It is suggested that the following diagram adequately depicts the tissue phase of schizogony as it occurs in malignant tertian malaria in man:

(Primary fever and recrudescences)
↑
Erythrocytic schizogony
↑
Sporozoite⟶Pre-erythrocytic schizogony

Comment and Conclusions

At the beginning of the present century the life cycle of the malaria parasite in man appeared to be completely known. It is a matter of considerable interest that, nearly half a century later, hiatuses in precise knowledge of the subject still exist. Despite the brilliant work of Shortt and his colleagues, only the pre-erythrocytic stage in *P. vivax* has so far been demonstrated in man. The technical difficulties associated with the production of hyperinfection in man and the demonstration of tissue schizonts in the liver have been overcome. No suitable laboratory animal is known which can be experimentally infected with any of the human species of malaria parasite, and in these circumstances the various problems concerning tissue forms are unlikely to be solved finally without the use of experimentally infected volunteers.

In the meantime the following tentative conclusions based mainly on indirect evidence are put forward regarding the tissue phase of the three species of malaria plasmodia commonly affecting man.

1. In benign tertian and quartan malaria there are both pre-erythrocytic and exo-erythrocytic stages of schizogony similar to those now known to occur in cynomolgi malaria in monkeys.

2. In vivax malaria characterized by short-term relapses such as are produced by the New Guinea or Chisson strains, normal exo-erythrocytic schizogony is maintained throughout the whole course of the disease and erythrocytic merozoites reach the circulating blood with regularity. Relapses cease when solid immunity and tolerance have developed or radical cure has been established.

3. In vivax infections characterized by long-term latency before relapse, such as is seen in infections with the St. Elizabeth, Madagascar, and Dutch strains, parasitaemia and immunity fail to become established during this initial latent period. As a working hypothesis it is suggested that during latency the exo-erythrocytic cycle is atypical, inasmuch as schizogony is switched over to the exclusive production of liver-invading merozoites, so that no erythrocytic merozoites reach the circulation. Latency ends when there is a reversion to normal exo-erythrocytic schizogony; this is indicated by the close relapse pattern which supervenes after the long period of latency has terminated in an overt malaria attack.

4. In malignant tertian malaria, after the pre-erythrocytic schizonts have ruptured and discharged their erythrocytic merozoites into the circulation on the seventh and possibly the eighth and ninth days as well, they disappear without giving rise to late exo-erythrocytic forms. The subsequent course of the disease will be determined solely by erythrocytic schizogony, and if parasitaemia is eradicated radical cure will result.

REFERENCES

Blackburn, C. R. B. (1948). *Trans. R. Soc. trop. Med. Hyg.*, **42**, 117.
Brumpt, E. (1937). *C.R. Soc. Biol., Paris*, **125**, 810.
Coatney, G. R., and Cooper, W. C. (1948). *J. Parasit.*, **34**, 275.
Cooper, W. C., Coatney, G. R., and Ruhe, D. S. (1947). *Amer. J. Hyg.*, **46**, 141.
Coulston, F., and Manwell, R. D. (1941). Ibid., **34**, 119.
Curd, F. H. S., Davey, D. G., and Rose, F. L. (1945). *Ann. trop. Med. Parasit.*, **39**, 208.
Davey, D. G. (1944). *Nature*, **153**, 110.
Fairley, N. H. (1945). *Trans. R. Soc. trop. Med. Hyg.*, **38**, 311.
—— *et al.* (1946). Ibid., **40**, 105.
—— *et al.* (1947). Ibid., **40**, 621.
Garnham, P. C. C. (1948). *Trop. Dis. Bull.*, **45**, 831.
Grassi, B. (1900). *R.C. Accad. Lincei.*, **3**, 289.
Hawking, F., Perry, W. L. M., and Thurston, J. P. (1948). *Lancet*, **1**, 783.
Huff, C. G., and Bloom, W. (1935). *J. infect. Dis.*, **57**, 315.
—— and Coulston, F. (1944). Ibid., **75**, 231.
James, S. P. (1931a). *Trans. R. Soc. trop. Med. Hyg.*, **24**, 477.
—— (1931b). *Proc. R. Acad. Med. Amst.*, **34**, 1424.
—— Nicol, W. D., and Shute, P. G. (1931). *Lancet*, **2**, 341
—— and Tate, P. (1937). *Nature*, **139**, 545.
—— —— (1938). *Parasitology*, **30**, 128.
Mudrow, L. (1940). *Arch. Schiffs- u. Tropenhyg.*, **44**, 257.
Porter, R. J. (1942). *J. infect. Dis.*, **71**, 1.
Raffaele, G. (1934). *Riv. Malariol.*, **13**, 332.
—— (1936). Ibid., **15**, 318.
Reichenow, E., and Mudrow, L. (1943). *Dtsch. Tropenmed. Z.*, **47**, 289.
Schaudinn, F. (1902). *Arb. GesundhAmt., Berl.*, **19**, 169.
Sergent, Et., and Sergent, Ed. (1922). *Arch. Inst. Pasteur Afr. N.*, **2**, 320.
Shortt, H. E., and Garnham, P. C. C. (1948). *British Medical Journal*, **1**, 1225.
—— —— Covell, G., and Shute, P. G. (1948). Ibid., **1**, 547.
—— —— and Maamos, B. (1948). Ibid., **1**, 192.
—— Menon, K. P., and Iyer, P. V. S. (1940). *Indian J. med. Res.*, **28**, 273.
Shute, P. G. (1946). *Trans. R. Soc. trop. Med. Hyg.*, **40**, 189.
Swellengrebel, N. H., and de Buck, A. (1938). *Malaria in the Netherlands*. 1st ed., p. 228. Scheltema and Holkema, Amsterdam.
Taliaferro, W. H., and Mulligan, H. W. (1937). *The Indian Medical Research Memoirs*, No. 29, pp. 1–138.
Tullis, J. L. (1947). *Amer. J. trop. Med.*, **27**, 21.
White, W. C., *et al.* (1948). *J. nat. Malaria Soc.*, **7**, 316.
Yorke, W. (1931). *Trans. R. Soc. trop. Med. Hyg.*, **24**, 526.
—— and Macfie, J. W. S. (1924). Ibid., **18**, 13.

CLINICAL VALUE OF PREGNANEDIOL ASSAYS*

BY

G. I. M. SWYER, M.A., D.M., D.Phil., M.R.C.P.

Endocrinologist, University College Hospital Medical School, London

A laboratory technique such as pregnanediol assay may lay claim to clinical value if it can be shown that its results yield information about diagnosis, prognosis, or treatment which will supplement that gained by unaided clinical examination. In assessing the clinical value of a given technique various factors must be considered and given due weight. The accuracy of the method, for example, is not of primary importance, though its ability to give unequivocal answers to the clinical questions posed is clearly a first requirement. Ease and speed of performance are significant considerations, and the nature and quantity of the clinical specimens required deserve attention. If to these we add the uniqueness of the information yielded by the technique, it should be possible to form an opinion of its value to the clinician in comparison with other laboratory procedures. In this paper the attempt is made to evaluate the position of pregnanediol assay, as judged by the above criteria and using the data that I have myself obtained.

A large number of different procedures for the assay of urinary pregnanediol have been described, some undoubtedly being far more accurate than others. I shall not attempt a comparative discussion of these rival methods, but certain general remarks are warranted. In the first place, methods requiring three or four days and many man-hours to complete are of little potential clinical value, no matter what their excellence as purely research techniques may be. Secondly, since by the nature of the clinical problems concerned repeated assays may be necessary, it becomes a matter of urgency to avoid, if at all possible, urine-collection requirements which would limit the application to in-patients only.

*Paper read at the British Congress of Obstetrics and Gynaecology, London, on July 6, 1949.

Clearly, few out-patients would co-operate to the extent of producing a weekly or fortnightly 24-hour urine collection, while the completeness of such collections as might be forthcoming would always be open to grave doubt. Great practical advantage would therefore be derived from the possibility of using first morning urine specimens rather than 24-hour collections, and it seemed reasonable to investigate such a possibility even though the variations in the results so obtained would be expected to be larger than those from 24-hour collections. With few exceptions, therefore, first morning specimens have been the rule throughout this investigation.

A final remark under this general heading may be made concerning the disadvantage, for clinical use, of methods which determine sodium pregnanediol glucuronidate, as compared with those which determine free pregnanediol. Any bacterial contamination may lead to hydrolysis of the glucuronidate and so give a spurious low value for the assay, and since in the hurly-burly of clinical medicine such contamination would be difficult to control, it seems wiser to avoid this potential cause of inaccuracy and to employ methods the results of which would not be vitiated in this way.

Considerations such as those outlined above led to the adoption, first of a modification of the Guterman (1944) technique (method I), and later of that described by Sommerville, Marrian, and Kellar (1948) (method II) after it had been shown (Swyer, 1949, wherein the details of the modification of the Guterman technique are described) that the method of Sommerville *et al.* was by almost all criteria the more preferable. Using these methods, an attempt has been made to study the clinical value of pregnanediol assay from the following points of view: (1) as a diagnostic test for pregnancy; (2) as a prognostic test in threatened abortion; (3) as a prognostic test for the likelihood of the initiation of labour by induction procedures; and (4) as a diagnostic aid in complications of pregnancy.

1. General Consideration of Results

For the purposes of this communication the results of a total of 858 pregnanediol assays are available for consideration. The details of these are set out in Table I, and the distribution of the values obtained is shown in the form of histograms in Fig. 1. The most striking feature of the latter is the considerable degree of overlap of values for pregnant and non-pregnant urines as obtained by both methods. The mode is shifted to the right in the case of method II, but apparently more so for pregnant than for non-pregnant urines. This is what would have been expected from the observations previously reported (Swyer, 1949), and is borne out by comparison of the two methods as pregnancy diagnosis tests (recorded below). The point which may be stressed is that, judging from the results as a whole, it cannot be expected that differentiation between pregnant and non-pregnant urines on the basis of their pregnanediol content will always be possible, so that the results in section 2 may be regarded as a fair sample of the overall results.

TABLE I.—*Broad Details of 858 Pregnanediol Assays*

Method	No. of Assays Performed		Totals
	Non-pregnant	Pregnant	
Modified Guterman	146	456	602
Sommerville, Marrian, and Kellar	49	207	256
Totals	195	663	858

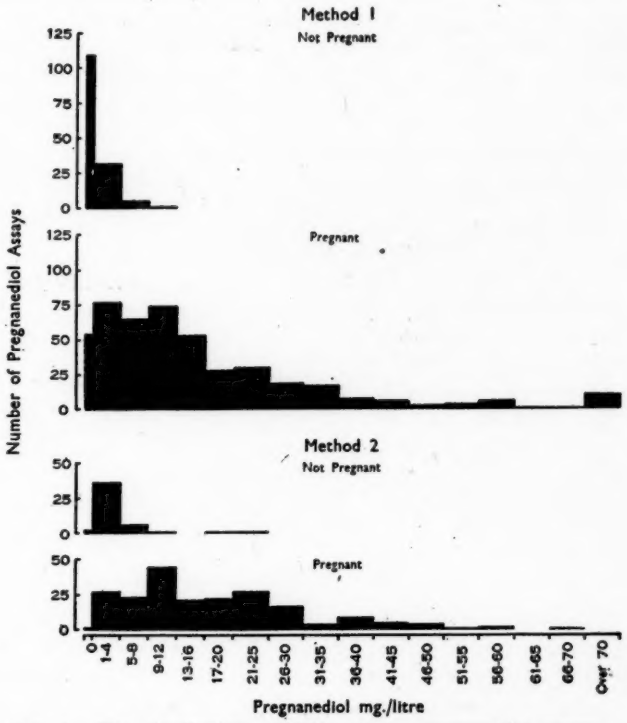


FIG. 1.—The distribution of 858 urinary pregnanediol assays.

2. Pregnanediol Assay as a Diagnostic Test for Pregnancy

The utilization of urinary pregnanediol assay as a basis for the diagnosis of pregnancy was first proposed by Guterman (1944, 1945), for which purpose he devised his rapid technique, which he did not, however, claim to be more than semi-quantitative. The high degree of accuracy for pregnancy diagnosis which Guterman found has not been uniformly achieved by other investigators (see discussion), and it was because of this that it was felt that yet another series might be desirable, especially one in which some other pregnancy diagnosis test of generally accepted validity was performed concomitantly with the pregnanediol assay on the same specimen of urine. For this purpose the Friedman test was selected, a standard quantity of 10 ml. of filtered urine being injected intravenously followed 48 hours later by sacrifice of the rabbit and examination of the ovaries for corpora lutea. All the specimens used in this series were actually sent for pregnancy diagnosis, so that in all cases there was some degree of clinical uncertainty. The subsequent fate of each was checked, and only those cases in which it was ascertainable have been included in the series.

For the first group of patients the modified Guterman procedure was used in 110 cases, and the results compared with the Friedman test are shown in Table II. In deciding whether the pregnanediol value was indicative of pregnancy or not, some level had to be chosen rather arbitrarily as the dividing-line. As a guide, assays were performed on the urines from 30 patients known to be non-pregnant, and

TABLE II.—*Concomitant Friedman Tests and Pregnanediol Assays (Method I) on 110 Urines Sent for Pregnancy Diagnosis (6 mg./litre Regarded as Minimal Value for Pregnancy)*

	Total	Friedman Test		Pregnanediol (Method I)	
		Correct	Incorrect	Correct	Incorrect
Pregnant ..	63	57 (90·5%)	6	26 (41%)	37
Non-pregnant ..	47	43 (91·5%)	4	44 (94%)	3
Totals ..	110	100 (91%)	10	70 (63·5%)	40

since the highest value found was 5 mg./litre, it was decided to regard 6 mg./litre as the minimal level for the diagnosis of pregnancy. Objections to this procedure could be cited, and because Guterman regards the "positive" colour in his test to be given by about 4 mg./litre of pregnanediol, the results have been recalculated on the basis of 4 mg./litre being the minimal level for pregnancy diagnosis (Table III). There is a slight improvement, but it is not sufficient for escape from the conclusion that, while false positives in non-pregnancy are rare, false negative pregnanediol values in pregnancy are so frequent as to condemn the test as an aid to pregnancy diagnosis.

TABLE III.—*The Results of Pregnanediol Assays (Method I), Previously shown in Table II, Recomputed on the Basis of 4 mg./litre as Minimal Value for Pregnancy*

	Total	Pregnanediol (Method I)	
		Correct	Incorrect
Pregnant	63	31 (49%)	32
Non-pregnant	47	43 (91·5%)	4
Totals	110	74 (67·3%)	36

Attention may be drawn to some of the cases in which discrepant results were obtained. There were two cases of proved hydatidiform mole, in both of which the Friedman test was positive (even when diluted 1/100, only 0.1 ml. of urine being injected); for the purposes of this comparison, these were interpreted as "false positive" Friedman tests, without any aspersions being cast upon the technical reliability of the test. In these cases the pregnanediol excretion was *nil* and 1 mg./litre respectively. Two other cases were clinically suspected as being those of hydatidiform mole; in one, in which the Friedman test was positive (though not on dilution) and the pregnanediol excretion was *nil*, subsequent events showed the case to be that of normal pregnancy; in the other, in which the Friedman test was negative and the pregnanediol excretion also was *nil*, no evidence either of pregnancy or of hydatidiform mole was obtained when the uterine contents were examined.

A specimen from a pregnant woman, when the period was only three days overdue, gave a negative Friedman test and contained 3 mg. of pregnanediol per litre; eight days later the Friedman test was still negative but the pregnanediol content had risen to 6 mg./litre. In a case which was subsequently proved to be that of ectopic pregnancy the Friedman test was negative and the pregnanediol excretion 4 mg./litre. In two cases of missed abortion the Friedman test was positive and the pregnanediol excretion 9.5 and 5 mg./litre. In neither case was a foetus found on evacuating the uterus. In three other cases "false negative" Friedman tests were obtained in cases of pregnancy; these must be regarded as technical faults. The corresponding pregnanediol levels were *nil* in two cases and 15 mg./litre in the third.

For the second group of patients, the procedure of Sommerville *et al.* (method II) was used in 101 cases, and the results, compared with the corresponding Friedman tests, are shown in Table IV. Once again 6 mg./litre is taken as the lowest permissible value for a "positive" pregnancy diagnosis, and it can be seen that the overall pregnanediol test results are considerably improved (82% correct) as compared with those in the previous series (63.5 or 67.3% according to the criterion of a "positive" value); that the reliability in pregnant cases is much greater (82.5 compared with 41 or 49%); but that a considerably larger number of "false positives" has now been produced (18.25% compared with 6%).

TABLE IV.—*Concomitant Friedman Tests and Pregnanediol Assays (Method II) on 101 Urines Sent for Pregnancy Diagnosis*

	Total	Friedman Test		Pregnanediol Assay	
		Correct	Incorrect	Correct	Incorrect
Pregnant ..	63	62 (98·5%)	1	52 (82·5%)	11
Non-pregnant ..	38	37 (97·5%)	1	31 (81·75%)	7
Totals ..	101	99 (98%)	2	83 (82%)	18

In this series there were three cases of missed or incomplete abortion; the Friedman test was positive in one, the pregnanediol value being 1 mg./litre, and negative in the other two, in which the pregnanediol values were 6 and 18 mg./litre respectively. There were, in addition, two cases of threatened abortion in which the diagnosis of pregnancy was uncertain at the time of testing; in one the Friedman test was negative, the pregnanediol value being 8 mg./litre and the patient aborted; in the other the Friedman test was positive, the pregnanediol value being 19 mg./litre and the pregnancy continued. A case of salpingitis which was considered clinically to have been possibly that of ectopic pregnancy had a pregnanediol excretion of 24 mg./litre; the Friedman test was negative.

3. Pregnanediol Assay as a Prognostic Test in Threatened Abortion

There have been several reports of the relation between pregnanediol excretion in cases of threatened abortion and the fate of the pregnancy (e.g., Hamblen, Cuyler, and Baptist, 1942; Guterman, 1946; Bender, 1947, 1948). The present series of cases is small compared with those of some previous authors, but the numbers are nevertheless sufficient for conclusions to be drawn which are not altogether in agreement with earlier reports.

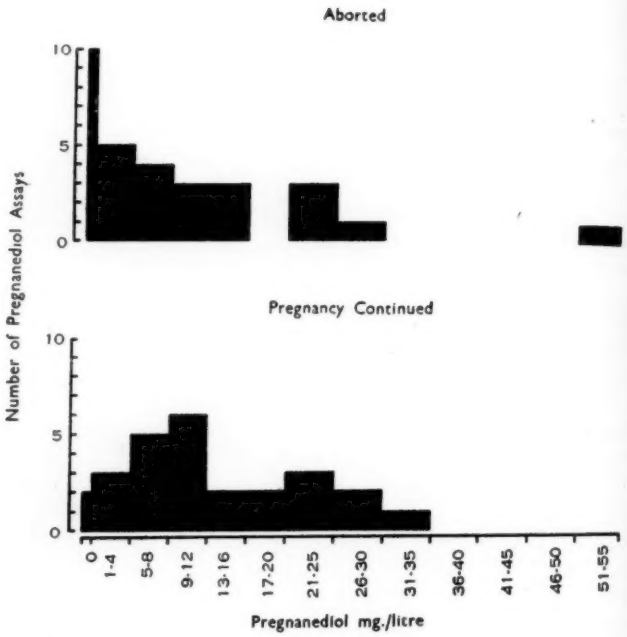


FIG. 2.—The distribution of 56 urinary pregnanediol assays from cases of threatened abortion.

Forty cases of threatened abortion have provided a total of 56 urine specimens for pregnanediol assay; the distribution of the values is shown in Fig. 2, where the cases are grouped into those that aborted and those that did not. The distributions are clearly different, but the overlap is

quite obvious. When the mean values for the two groups are compared by the t test, the following result is obtained:

Mean value for abortion group .. .. 8.733 mg./litre
" " " non-abortion group .. 12.4 "
n=54; t=2.579 (P<0.02>0.01)

It may therefore be concluded that the pregnanediol values in cases of threatened abortion are, in general, higher when the pregnancy is going to continue than when it is going to terminate, and that the chances of a difference between the means such as that observed occurring on a purely random sampling basis from a homogeneous population are more than 1 in 50 though less than 1 in 100 against.

The clinician, however, is more interested in individual cases than in the behaviour of patients with threatened abortion in general, and it is therefore of importance to consider the ability of the test to predict the outcome in individual cases. A pregnanediol value of 6 mg./litre has again been taken as the minimum for predicting continuation of the pregnancy, and the findings are set out in Table V, both on the basis of the first reading and, where

TABLE V.—*Prediction of the Fate of Cases of Threatened Abortion on the Basis of Pregnanediol Excretion*

	First Reading			Final Assessment		
	Pregnancy Continued	Aborted	Total	Pregnancy Continued	Aborted	Total
Correct ..	12	14	26	14	15	29
Incorrect ..	5	9	14	3	8	11
Totals ..	17	23	40	17	23	40

more than one assay was performed, on the basis of the final assessment, a rising pregnanediol titre being taken as indicative of continuation of pregnancy. The correct prediction was given in 29 out of 40 cases in the final assessment (72.5%). Of the 40 cases, 57.5% aborted; of those that did not, 14 out of 17 had satisfactory or rising pregnanediol titres, but of the 23 patients who aborted, eight also had satisfactory pregnanediol titres.

4. Pregnanediol Assay as a Prognostic Test for the Likelihood of the Initiation of Labour by Induction Procedures

Since most observers agree that the spontaneous onset of labour is ordinarily preceded by a pronounced fall in the pregnanediol excretion, it seemed worth while to investigate the excretion in patients in whom, for various clinical reasons, it was desired to induce labour and to see what correlation, if any, existed between the amount of pregnanediol excreted and the effect of the induction procedure. This has been done in 10 patients, the results being shown in Table VI, in which the cases are recorded in ascending order of pregnanediol excretion.

TABLE VI.—*Pregnanediol Assays in Patients on whom Induction Procedures were Performed or Contemplated and the Results of Those Procedures*

Case No.	Pregnanediol	Mode of Induction	Result
1	10·5 mg./24 hrs.	O.B.E.	Delivery
2	19·4 "	Spontaneous delivery	
3	23 mg./litre	High puncture	Delivery
4	25·2 mg./24 hrs.	O.B.E.	"
5	41 "	Spontaneous delivery	
6	49 "	O.B.E.	Delivery
7	49·7 "	O.B.E.	Nil
8	55·5 "	O.B.E.	Delivery
9	56 "	O.B.E.	Nil
10	57 "	Repeated 2 days later	Delivery
		Spontaneous delivery	

O.B.E. = Induction by castor oil, bath, and enema.

It is interesting to note that in three cases spontaneous labour began *before* the induction procedure was started, with pregnanediol excretions ranging from 19.4 to 57 mg. in the preceding 24 hours. On the other hand, the excretions in the two failures were both high—49.7 and 56 mg./24 hours respectively. It would seem, therefore, that, although induction is less likely to succeed at high levels of pregnanediol excretion, the prediction of the fate of a given case cannot be accurately made on the basis of pregnanediol assay.

5. Pregnanediol Assay as a Diagnostic Aid in Complications of Pregnancy

With a view to investigating the possible value of pregnanediol assay as a diagnostic aid in various complications of pregnancy 41 such assays were carried out on specimens obtained from 17 patients with various complications. The details are set out in Table VII, and the following comments seem justifiable: in cases of missed abortion variable values may be found, some "positive" and others "negative";

TABLE VII.—*Pregnanediol Assays in Various Complications of Pregnancy*

Case No.	Diagnosis	Pregnanediol mg./litre	Remarks
1	Missed abortion ..	9, 4, 3, 0	Friedman test positive. Curettage showed surviving placental tissue but no embryo
2	" " ..	0, 5	Friedman test positive; no embryo found on curettage
3	" " ..	8	
4	" " ..	8	
5	? Incomplete abortion	10	Friedman positive; pregnancy continued
6	Hydatidiform mole ..	0	Confirmed by curettage
7	" "	0, 1	" "
8	? Hydatidiform mole	11	Friedman test positive undiluted only; normal pregnancy
9	" " "	0	" " "
10	" " "	0	Friedman test negative; non-pregnant
11	Ante-partum haemorrhage at 35 weeks	43, 38, 60, 23, 45	Daily pregnanediol assays; pregnancy went to term
12	Ante-partum haemorrhage at 37 weeks	60, 69, 51, 54, 16	" " "
13	Pyelitis at 29 weeks ..	34	Pregnancy continued
14	Ectopic pregnancy ..	4	Friedman test negative; confirmed at laparotomy
15	Double uterus ..	33	
16	Polycystic ovary: punctured at 8 weeks	0, 5, 10, 31, 10, 9, 7, 9, 10	Daily pregnanediol assays: pregnancy continued
17	Dystocia dystrophia	92, 128, 78, 154	Daily pregnanediol assays at full term

the Friedman test may also be positive or negative, and it cannot be claimed that either test, or the two in combination, enables a definite diagnosis to be reached.

In both cases of proved hydatidiform mole the pregnanediol excretion was trivial, while chorionic gonadotropin was present in the usual large amounts. On the other hand, Case 8, clinically considered to be one of hydatidiform mole, was found to have both Friedman test and pregnanediol assay within the limits of normal pregnancy, and such it eventually proved to be. In Cases 9 and 10 hydatidiform mole was again suspected clinically; pregnanediol excretion was *nil* in both cases, but in one the Friedman test was positive undiluted only and normal pregnancy was the eventual conclusion, while in the other the Friedman test was negative and no further evidence of pregnancy was forthcoming.

The two cases of ante-partum haemorrhage showed pregnanediol excretions within normal limits for the periods of gestation, and the same applies to the case of pyelitis at the 29th week of gestation. In the case of ectopic pregnancy, both the Friedman test and the pregnanediol assay was misleading. The pregnanediol excretion in Case 16—that of polycystic ovary punctured at 8th week

of gestation—showed that the operation had not interfered with progesterone production and, accordingly, the pregnancy proceeded normally. In the last case—that of dystocia dystrophia—the pregnanediol excretion seemed to be excessive in view of the fact that labour, albeit of an ineffective type, had already begun.

Discussion

Before discussing the results reported above, it would seem desirable to point out why no mention has so far been made of the use of pregnanediol assay as a means of detecting ovulation in non-pregnant women. Sufficient studies have been made by various workers (e.g., Venning and Browne, 1937a, 1937b; Stover and Pratt, 1939; Hamblen, Cuyler, and Baptist, 1942, etc.) of the pregnanediol excretion during the luteal phase of the menstrual cycle to make it abundantly clear that the total excretion is so variable, and may be so small in apparently normal cycles, that only accurate techniques employed on complete collections of urine extending over several days (even the complete luteal phase) could hope to give indubitable evidence of corpus luteum activity. These requirements place the method entirely outside the realms of clinical practicability, and when it is granted that the basal body temperature record and the endometrial biopsy can give highly reliable results with very little effort, it must be conceded that pregnanediol assay can have no clinical value for this purpose.

The advantages claimed for pregnanediol assay as a diagnostic test for pregnancy were its rapidity (some three hours only are required for the Guterman method) and that it eliminates the inconvenience and expense of animal tests. The accuracy claimed by Guterman (1945) was 92.7% for 248 cases, the Friedman test in 201 of these being only 87.1% correct. Apart from McCormack (1946), who found complete agreement between pregnanediol assays and Friedman tests in 266 cases, no other observers seem to have achieved results at all comparable with these.

It is instructive to compare the published figures of the above authors with those of Reinhart and Barnes (1946) and Merivale (1948); this is done in Table VIII, which

TABLE VIII.—*Comparison of the Published Results of Various Authors with Pregnanediol Assay as a Pregnancy Diagnosis Test*

Author	No. of Patients	Percentage Accuracy	
		Pregnanediol Test	Friedman Test
Guterman	248	92·7	87·1
McCormack*	266	99·0	99·0
Reinhart and Barnes ..	130	69·2	—
Merivale	105	63·8	—
Swyer, Series I	110	67·5	91·0
„ „ II	101	82·0	98·0

* Omitting 30 cases of threatened abortion, all with negative pregnanediol and positive Friedman tests.

gives the overall accuracy figures. It is evident at once that there is close agreement between the results of Reinhart and Barnes, Merivale, and the first series reported in this communication, and gross disagreement of these findings with those of Guterman and of McCormack. Guterman (1945) has pointed out that his test should be restricted to patients with amenorrhoea who have not received progesterone therapy, but, as Reinhart and Barnes observe, the elimination of patients with vaginal bleeding or those who have received progesterone therapy materially limits the value of the test for routine clinical use.

Although in most of the published series the proportion of false positives is relatively low (that of Reinhart and Barnes is an exception), such results can be obtained in a variety of conditions—for example, the luteal phase of the menstrual cycle, which, if prolonged by a lengthened proliferative phase, might well lead to the clinical suspicion of pregnancy; corpus luteum cysts (Guterman, 1945; McCormack, 1946; Bender, 1948); arrhenoblastoma; a case of amenorrhoea with uterine enlargement due to metastatic carcinoma; and a case of salpingitis diagnosed clinically as ectopic pregnancy (Morrow and Benua, 1946). This last case is interesting in so far as it compares with a somewhat similar case reported in this paper, also with a "positive" pregnanediol excretion (24 mg./litre).

When all the available evidence is considered it seems impossible to escape the conclusion that the reliability of pregnanediol excretion is insufficient to warrant its use as a clinical method for pregnancy diagnosis. In its main claim, that of rapidity and convenience, it bears no comparison with the male-toad test, and, provided a supply of suitable animals can be assured, this test, or one of its modifications, would seem to fulfil all the requirements for clinical use.

Regarding the prediction of the fate of threatened abortion, once again the accuracy reported in the present series is far less than that claimed by Guterman (1946) (72.5% correct for 40 cases as compared with 93% for 73 cases). Bender (1948), however, has produced evidence that, using the Guterman test to differentiate cases of threatened abortion with high pregnanediol excretion from those with low outputs, and reserving treatment with progesterone for the latter only, a statistically significant increase in the salvage rate can be obtained; on the other hand, progesterone given to patients with threatened abortion with positive Guterman tests increased the likelihood of abortion. If this work can be substantiated, it would seem to be a really valid clinical application of pregnanediol assay. It is right, however, to point out that the administrative difficulty of obtaining the result of the test promptly, together with the necessity to wait for the first morning urine sample, may lead to delay in the exhibition of progesterone in those cases that warrant it, the abortion perhaps becoming inevitable as a result.

In the diagnosis of complications of pregnancy, the results presented do not suggest that pregnanediol assays are likely to prove of much value except in the case of hydatidiform mole, in which pregnanediol seems to be absent from the urine. It is true that it would be impertinent to attempt to generalize from the findings in two cases only, but on this point confirmatory support is to be obtained from other sources: Guterman (1945) found negative tests in three cases of hydatidiform mole, while McCormack (1946) reported the same results in two other cases. On the basis of seven cases, therefore, it would seem reasonable to suggest that absence of urinary pregnanediol in a case clinically suspected as being hydatidiform mole and giving a positive test for chorionic gonadotropin in high dilution, very substantially supports the diagnosis.* Such a confirmation may be of great value at about the twelfth week of gestation, or in the case of multiple pregnancy, in both of which conditions the gonadotropin excretion may normally be so high as to give a positive Friedman test at 1/100 dilution.

If now the clinical value of pregnanediol assay is judged from the evidence presented on the basis of the criteria laid down in the introduction to this paper, it must be con-

*Since reading the proofs of this paper, the author has had a third case of hydatidiform mole with a positive Friedman test at 1/100 dilution and absence of urinary pregnanediol. Dr. S. Bender, however, has encountered two out of three cases of hydatidiform mole with "positive" pregnanediol excretions.

cluded that, in general, it has little to offer the practising clinician. It seems doubtful whether the relative inaccuracy of the methods suitable for clinical application can be held completely responsible for this state of affairs; rather should one ascribe it to the inherent variability of pregnanediol excretion both in the same and in different patients. Consideration of the factors responsible for this variability is beyond the scope of the present discussion, but it does seem permissible to observe that there are no solid grounds for believing that pregnanediol excretion reflects at all closely the progesterone levels of the blood, and undoubtedly the latter are of far the greater physiological significance. Simple direct means of assessing the blood progesterone would surely supply evidence of much more clinical value than could ever be expected from the pregnanediol excretion in the urine.

My sincere thanks are due to the members of the staff of the Obstetric Unit for their generous co-operation in these studies, and to Mr. A. A. Cernik for carrying out a large number of the assays, the results of which are recorded above.

REFERENCES

Bender, S. (1947). *J. Obstet. Gynaec. Brit. Emp.*, **54**, 783.
—— (1948). *British Medical Journal*, **1**, 683.
Guterman, H. S. (1944). *J. clin. Endocrinol.*, **4**, 262.
—— (1945). Ibid., **5**, 407.
—— (1946). *J. Amer. med. Ass.*, **131**, 378.
Hamblen, E. C., Cuyler, W. K., and Baptist, M. (1942). *Amer. J. Obstet. Gynec.*, **44**, 442.
McCormack, G. (1946). Ibid., **51**, 722.
Merivale, W. H. H. (1948). *British Medical Journal*, **1**, 685.
Morrow, A. G., and Benua, R. S. (1946). *Amer. J. Obstet. Gynec.*, **51**, 685.
Reinhart, H. L., and Barnes, A. C. (1946). *J. clin. Endocrinol.*, **6**, 664.
Sommerville, I. F., Marrian, G. F., and Kellar, R. J. (1948). *Lancet*, **2**, 89.
Stover, R. F., and Pratt, J. P. (1939). *Endocrinology*, **24**, 29.
Swyer, G. I. M. (1949). *Lancet*, **1**, 104.
Venning, E. M., and Browne, J. S. L. (1937a). *Amer. J. Physiol.*, **119**, 417.
—— —— (1937b). *Endocrinology*, **21**, 711.

VESICO-BULLOUS DISEASES AFFECTING THE EYE*

BY

ALICE CARLETON, M.D.

(From the Department of Dermatology, Radcliffe Infirmary, Oxford)

There are few skin diseases which may not at some time involve the eye and its appendages. It is impossible to consider all of them here, even in the most summary way. I propose instead to survey a single group—the vesico-bullous diseases of internal origin—affecting the skin and mucous membranes. Even with this restriction the survey must necessarily be a brief one.

The more one considers the vesico-bullous diseases the more one is struck not by their clinical differences but rather by their essential similarities. A common factor seems to operate in all of them, producing a particular type of cell reaction. It is this which makes a study of the group of special interest. In some diseases a virus, in others an unknown toxin, exercises a destructive action on the mucosae or on the deeper cells of the epidermis, with resultant cellular liquefaction. This seems to release a physico-chemical force, which in turn increases capillary permeability and attracts the filtrate as well as the local tissue fluid to the injured area. In this way a vesicle is formed. When the hydrostatic pressure within the vesicle has reached a certain point the movement of the fluid is checked. Whether the vesicle breaks down to form an oozing erosion or not depends largely on the thickness of its roof. Naturally, in the conjunctivae and other mucous membranes the covering is thin and the vesicles are correspondingly transient, so that the clinical picture is a raw oozing surface, whereas the skin may still show intact vesicles. But though the distribution and clinical appearance in the different diseases of this group are varied and characteristic, histologically we can distinguish only grades of severity in an essentially similar reaction.

Percival and Hannay (1949) have published an excellent study of the pathology of bullous formation, from which the following interesting sentence is taken: "To state the problem differently, it can be asked why the exudate remains in the dermis in urticaria, becomes localized at the dermo-epidermic junction in dermatitis herpetiformis, in the rete mucosum in eczema, and under the stratum corneum in pemphigus foliaceus, when the mechanism which made the exudate available is common to all four conditions, and is in all probability initiated by a common factor."

The diseases of this group which affect the eye are: herpes simplex; herpes zoster; erythema multiforme, including the severe form known as the Stevens–Johnson syndrome; foot-and-mouth disease; Touraine's aphthosis; dermatitis herpetiformis; and pemphigus. (Conjunctival scarring is associated with other skin diseases, such as bullous eruptions following vaccination, erythroderma ichthyosiforme of Brocq in its bullous form, epidermolysis bullosa dystrophica acquisita, and congenital syphilis, but these conditions do not belong to the group under consideration.)

Herpes Simplex

This well-known disease is characterized by the often-repeated occurrence of little groups of blisters on a base of oedema and redness. Its virus origin is amply proved, and corneal inoculation of a rabbit gives positive results. In contrast with what occurs in many virus diseases the host develops no immunity. On the contrary, a local hypersensitivity often causes the same small patch to respond on each occasion. The lips and face are most frequently affected, but lids, conjunctiva, or cornea may suffer instead.

The evidence suggests that the virus is a saprophyte living in happy matrimony with the tissues until a *tertium quid* disturbs the harmony. This may be any one of a variety of agents which include cold, heat, sunlight, food, drugs, and bodily upsets. The injured cell then goes through the processes of liquefaction and vesicle formation already described. Individual eruptions heal easily and need only to be kept clean. But to prevent recurrence is a difficult matter. Irradiation of the affected area of skin with *x* rays may produce an alteration which increases local immunity, or repeated inoculations with smallpox vaccine may raise the general resistance, but disappointing results are common.

Herpes Zoster

This complaint is not transmissible by inoculation. But as specific antibodies have been found in the blood, and inclusion bodies have been demonstrated in the vesicles, the evidence is in favour of a virus disease. The cutaneous reaction is greater and deeper than in herpes simplex. Haemorrhagic, purulent, or necrotic vesicles may occur and leave severe scarring. Many cases have been described as

*Read in the Section of Ophthalmology at the Annual Meeting of the British Medical Association, Harrogate, 1949.

sequelae of nerve infection or injury. So that here, again, it seems that a cell injury may open the door to a virus attack.

Herpes zoster is of special importance when it affects the eye, because of the risk of permanent injury. Becker (1948) has published a paper claiming good results in this condition by the injection of blood or serum from people who have recovered from the disease. This was for some time thought to be useless, because of statements such as that of Rivers (1939) that "convalescent blood or serum is of no value in the therapy of virus diseases, because by the time the disease is evident the organism has already penetrated the cell, a barrier which no antibody can transgress." Despite this view the method seems to give hopeful results. Becker used blood transfusions, blood plasma, and whole blood injections, with material taken from a donor any time from three weeks to two years after his having the disease.

Erythema Exudativum Multiforme

In 1866 Ferdinand Hebra described a disease affecting the face, the limbs, and sometimes the mucosae. The rash, as the name suggests, takes on many forms, such as macules, weals, bullae, or large annular or serpiginous plaques, of an angry blue-red colour. The eruption is short-lived but often recurrent. A somewhat similar rash, more rosy in colour and more varied in its distribution, can be elicited by a wide range of toxins. It is not clear whether Hebra's erythema multiforme is a specific entity or not. Ocular involvement generally takes the form of a pseudo-membranous conjunctivitis which may lead to shrinkage or uveitis. Lacrimation and photophobia are also seen, and corneal ulceration and perforation have been described. No causative agent has been found.

In 1922 Stevens and Johnson described a severe form of erythema multiforme which, in English-speaking countries, is now generally known under their name. An earlier account had, in fact, already been published by Rendu in 1916 under the name of "ectodermose érosive superficielle," and the condition is also referred to as "dermatostomatitis" or "eruptive fever with ophthalmia." This begins acutely with a rash like erythema multiforme, but the general symptoms are much more severe and the patient is feverish and looks gravely ill. The eyes, mouth, and genital mucosae are so inflamed and eroded as to be extremely tender, so that micturition becomes an ordeal and feeding may have to be done through a tube. Despite this disturbing start, improvement takes place in a week or ten days, and recovery is usual in about three weeks. Unfortunately, the eyes may be irreparably damaged. The conjunctivitis may leave adhesions or scars, or the corneal damage may end in opacities or in perforation. An effort should be made to keep the lids open with tiny strips of adhesive tape, but on account of the photophopia the patient is apt to struggle against this.

Patz (1947) made a study of six cases. He tried various methods of discovering a virus by making smears from the conjunctiva and vagina, by complement-fixation tests with psittacosis antigen, by cultures in chick embryos, and by the intracerebral and intraperitoneal injection of vesicular fluid into rabbits, guinea-pigs, and mice. All results were negative.

Vincent's stomatitis has been found associated with erythema multiforme in three cases, and it was suggested that the fuso-spirochaete, by altering tissue sensitivity, might lead to the Stevens–Johnson syndrome. But proof of this is not forthcoming, and the association of the two complaints has scarcely ever been found.

Anderson and his colleagues (1949) claim to have found a virus with cytoplasmic inclusion bodies following rabbit cornea inoculation. Their study was limited to one case.

Treatment is symptomatic. Nicotinic acid is said to be of use, but as most cases clear up spontaneously it is difficult to be sure of its value.

Foot-and-Mouth Disease ("Fièvre Aphtheuse")

This may be acquired by direct contact with infected animals or, less often, by drinking their milk. The distribution is not unlike the preceding condition, but the skin around the nails is chiefly affected and the lips and mouth are dry and burning, whereas in the Stevens–Johnson syndrome lesions are more often seen on the wrists and ankles, and there is profuse salivation. Ocular involvement is not common. If there is any difficulty in diagnosis, guinea-pig inoculation in foot-and-mouth disease gives a positive result.

Touraine's Aphthosis

There is a fearsome dermatological jungle in which various diseases with resounding eponymous titles struggle for life. They are the chronic erosive conditions affecting the eyes, mouth, and genitalia. Each specialist is naturally absorbed in his own field, which for him takes precedence of all others, and so a number of syndromes have arisen, such as Sutton's (1911) "periadenitis mucosae necrotica recurrens," Loblowitz's (1910) "ulcus neuroticum oris et vulvae," Lipschütz's (1923) "acute vulval ulcer," "pustulo-ulcerous balanitis," and others. Behcet (1937, 1940), a Turkish dermatologist, described a triple symptom-complex in which all three areas—eyes, mouth, and genitalia—are affected simultaneously or in sequence. Little round or oval ulcers with yellow sloughs succeed one another in the mouth, vulva, or glans penis, associated with inflammation of the cornea, conjunctivitis, or sclera. The skin has a tendency to develop acneiform pustules or deep-seated lesions of the erythema nodosum type.

In 1941 Touraine made an extensive study of this whole group. He suggests that the various conditions belong to one single systemic disease, which he ascribes to an ultra-virus, and to which he gives the name "aphthosis." He thinks that this agent, like the virus of herpes simplex, becomes established in the body and manifests itself clinically when for divers reasons the individual becomes anergic. Touraine divides his aphthosis into three groups according to severity and extent.

1. A generalized form, affecting the skin, mucosae, and joints. This is severe and starts with fever and general systemic disturbance.

2. A milder form, involving the mouth and genitalia, with a few scattered vesico-pustules on the skin.

3. Aphthosis of the mucosae alone, in the form of small recurrent ulcers, or, less often, a single large ulcerative area, which may be mistaken for a venereal infection. There is much variety in the severity and duration of the ulcers, and also in the length of the free periods. Recurrences may be precipitated by any bodily upset, such as infectious fevers or pregnancy, or by local trauma or operative procedure.

Touraine's view is substantially in accord with Whitwell's (1934) conception of "embolic showers" causing necrotic apthae in mucosae and skin. It may be that future research will show the conception of "aphthosis" to have over-simplified the problem. But until further knowledge is obtained the harassed dermatologist can only feel relief at having so many odd sheep neatly penned into one fold.

Dermatitis Herpetiformis

It is unnecessary to dwell on the clinical appearance of this well-known disease, particularly as the eyes are rarely affected. Only a few points of special interest will be mentioned. There is a special sensitivity to iodine, and in one case involving the eyes and nasopharynx painting with iodotannic spirit produced a disastrous exacerbation. There is some evidence that hypersensitivity to a bacterial toxin may be an important aetiological factor. It is often possible to control the disease, and sometimes even to cure it, by long-continued small doses of sulphapyridine. The aim is to raise the resistance of the body rather than to eliminate the supposed toxin.

Pemphigus

The cause of pemphigus is unknown, and it follows that the validity of the different divisions or varieties is still uncertain. Dermatologists, however, clearly distinguish between four clinical types—acute pemphigus, chronic pemphigus or pemphigus vulgaris, pemphigus foliaceus, and pemphigus vegetans. Acute pemphigus is a fulminating disease generally occurring in people who handle animal carcasses. It begins on the hand and spreads over the whole body, leading rapidly to death in 80 to 90% of cases. In pemphigus vulgaris the development is more insidious, but, according to Lever and Talbott (1942), death occurs in 83% within one year of onset and in 97% within two years. It follows from these figures that treatment does no more than alleviate the symptoms. Grace and Hellman (1946), however, claim to have cured two cases of pemphigus vulgaris with blood transfusions from two patients who had recovered. One cannot generalize on the strength of two cases, but as spontaneous cure is rare this claim is of great interest.

A brief survey of the literature on ocular pemphigus reveals an almost inextricable confusion, and the term is manifestly used in the loosest way. One author talks of "ocular pemphigus" under one heading and "pemphigus vulgaris with ocular involvement" under another. A different prognosis and a different racial distribution are given, but no criteria for distinguishing one from the other. Klauder and Cowan (1942) have stated the issue clearly. They use the original term "essential shrinkage of the conjunctiva," and believe that this occurs in a number of dermatoses, of which some are very rare. The list includes: severe erythema multiforme or the Stevens–Johnson syndrome; bullous eruptions following vaccination; erythroderma ichthyosiforme of Brocq in its bullous form; dermatitis herpetiformis; epidermolysis bullosa dystrophica acquisita; and congenital syphilis.

Klauder and Cowan would confine the term "ocular pemphigus" to a benign affection of old age often associated with pemphigus of the nasopharynx and with a trivial bullous eruption of the skin, especially of the lids and face. The genitalia may also be involved. It is not found more often in Jew than in Gentile, though, as is well known, the Jewish race is particularly sensitive to pemphigus vulgaris. The question therefore remains to be answered, Is ocular pemphigus a special entity with a benign course, occurring late in life and with no particular racial distribution, or is it a mild form of pemphigus vulgaris, to which disease Jews are so sensitive that if affected at all they develop the severe form?

Discussion

A group of diseases exist which produce vesicles or bullae, breaking down into erosions of the skin or mucous membranes. Despite clinical differences the histopathology is essentially similar throughout the group. Some are caused by viruses; in some no virus origin can be discovered. A connecting thread seems to run through the group, as shown by a symmetry of distribution and a susceptibility to precipitating factors of many different kinds which alter the reactivity of the cell and lead to its liquefaction. Somewhere in this complexity we should be able to find the master key which would fit all the doors. It may be that this will be given to us by research in pure science, and, indeed, this seems already possible. Before the war Peters (1936), considering the biochemistry of the cell and the perpetual shuttle of its metabolic life, made an incidental note of the fact that very small quantities of arsenic could, as it were, stop a cell "breathing" by interfering with one of its enzyme systems—the pyruvate oxidase system, which is instrumental in breaking down glycogen or glucose into carbon dioxide and water. At the onset of war, when scientists were directed to problems of immediate practical importance, the Department of Biochemistry at Oxford, under the charge of Professor Peters, began to consider possible antidotes to arsenical poisoning in the form of lewisite. This earlier observation provided a starting-point for research, and in a short time Thompson (quoted by Carleton *et al.*, 1946) discovered that a dithiol—dimercaptopropanol—could combine with arsenic and even remove it from the cell, to be harmlessly excreted in the urine.

Now, acute arsenical dermatitis has features not unlike the diseases we have been considering. A drop of lewisite on the skin brings out a large bulla. In the conjunctiva it produces a penetrating destruction of the eye. In arsenical poisoning, such as may arise in the treatment of syphilis, bright-red blotches appear on the limbs and spread to a generalized exfoliative dermatitis. Interference with a single enzyme system can therefore cause cellular liquefaction and breakdown. A known poison acting in an understood manner produces results which are partly reversible by an antidote of known chemical composition. In the vesico-bullous diseases, we know neither the poison nor its precise manner of acting, still less the antidote. But we have here an excellent example of the fruitfulness of correlating clinical with purely scientific research in the solution of our joint problems.

REFERENCES

Anderson, J. A., Bolin, V., Sutow, W. W., and Kitto, W. (1949). *Arch. Derm. Syph., Chicago*, **59**, 251.
Becker, F. T. (1948). Ibid., **58**, 265.
Behcet, H. (1937). *Derm. Wschr.*, **105**, 1152.
—— (1940). *Dermatologica*, **81**, 73.
Carleton, A., Peters, R. A., Stocken, L. A., Thompson, R. H. S., and Williams, D. I. (1946). *J. clin. Invest.*, **25**, 497.
Grace, A. W., and Hellman, L. D. (1946). *Arch. Derm. Syph., Chicago*, **53**, 249.
Hebra, F. (1866). *Diseases of the Skin*. Trans. by C. Hilton Fagge. New Sydenham Society, vol. 1, 285.
Klauder, J. V., and Cowan, A. (1942). *Amer. J. Ophthal.*, **25**, 643.
Lever, W. F., and Talbott, J. H. (1942). *Arch. Derm. Syph., Chicago*, **46**, 348.
Lipschütz, B. (1923). *Dermatologische Studien*. L. Voss, Leipzig.
Loblowitz, J. (1910). *Arch. Derm. Syph., Wien*, **102**, 191.
Patz, A. (1947). *New Engl. J. Med.*, **236**, 697.
Percival, G. H., and Hannay, P. W. (1949). *Brit. J. Derm. Syph.*, **61**, 41, 77.
Peters, R. A. (1936). *Nature*, **138**, 327.
Rendu, R. (1916). *Rev. gén. Clin.*, **30**, 351.
Rivers, T. M. (1939). *Viruses and Virus Diseases*. Stanford University Press.
Stevens, A. M., and Johnson, F. C. (1922). *Amer. J. Dis. Child.*, **24**, 526.
Sutton, R. L. (1911). *J. cutan. Dis.*, **29**, 65.
Touraine, A. (1941). *Bull. Soc. franç. Derm. Syph.*, **48**, 61.
Whitwell, G. P. B. (1934). *Brit. J. Derm. Syph.*, **46**, 414.

RETINAL ARTERIAL OCCLUSION IN MIGRAINE

BY

G. S. GRAVESON, M.A., M.D., M.R.C.P.

Lecturer in Neurology, University of Manchester

(From the Department of Neurology, Manchester Royal Infirmary)

The occurrence of retinal arterial spasm in the early phases of attacks of migraine has occasionally been described. Unfortunately, an opportunity of examining the optic fundi at such times seldom presents itself, and therefore the frequency and distribution of arterial changes are unknown.

When retinal spasm is severe an occlusion of the affected vessel may occur, leading to a permanent defect in the field of vision. This is a rare complication, but one of much greater theoretical importance than its infrequency would suggest. Such cases supply direct evidence that the pre-headache phenomena of migraine are due to vasospasm. For this reason the following cases are worth recording.

Case 1

A girl aged 17 first attended hospital in April, 1948. From the age of 7 she has had periodic "bilious attacks" without headache. Her attacks of migraine began early in 1947 and have occurred at approximately monthly intervals. Until March, 1948, they were all similar in type, beginning with a whirling sensation surrounded by coloured lights and zigzag formations which started in both eyes simultaneously in the temporal half of the fields and spread to involve central vision. This teichopsia usually lasted about 10 minutes and disappeared suddenly, to be succeeded sometimes by a throbbing headache situated in the fronto-temporal region on both sides. The headache was equally short-lived, never lasting longer than about a quarter of an hour.

In March, 1948, she suddenly developed a blurring of vision in the right eye and thought that one of her usual attacks was starting. Instead the blur persisted and no headache followed. She noticed that the visual defect was present only in the right eye, and that it was situated below and to the left of whatever she looked at. It had remained unchanged for three weeks before her first visit to hospital.

Examination.—The only abnormalities to be found were in the right eye. Ophthalmoscopy revealed an occlusion of the superior temporal retinal artery at a point about half a disk diameter from where it crossed the disk margin. From this point the vessel continued as a fine thread from which no light reflex was seen. In the macular area just above the fovea there was a small area of retinal oedema. The disk itself was normal. The field of vision showed a hemianopic defect in the lower half-field, especially on the nasal side (Fig. 1). This did not involve the fixation point, so that her visual acuity remained normal: 6/5 J1. Her cardiovascular system was normal; the blood pressure was 130/85. Blood Wassermann reaction was negative. There was no family history of migraine.

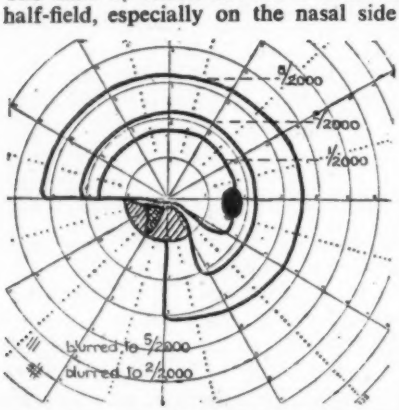


FIG. 1—Case 1. Field of vision of right eye, April, 1948: showing a defect in the lower half-field, particularly on the nasal side, together with a paracentral relative scotoma in this sector.

She was seen again in December, 1948. In the intervening nine months she had had eight further attacks of migraine—all consisting of headache preceded by scintillating scotoma formation in both visual fields. The defect in the right visual field had improved a little and was now confined to the inferior nasal quadrant (Fig. 2). Fundal examination still showed an occlusion of the superior temporal retinal artery, and the superior temporal portion of the optic nerve-head was now pathologically pale. The macular oedema had disappeared. Her visual acuity remained 6/5 J1 in the right eye.

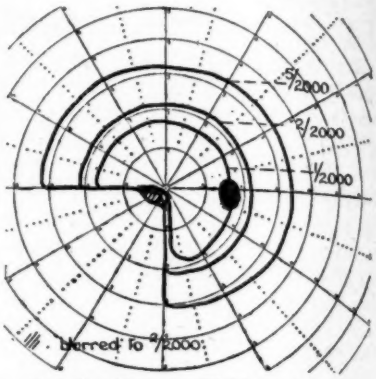


FIG. 2.—Case 1. Field of vision right eye, December, 1948: showing improvement in both the sector defect and the relative scotoma.

Case 2

A woman aged 35 was first seen in October, 1948, complaining of impaired vision in the right eye. For the previous two years she had suffered from attacks of migraine at approximately monthly intervals. These attacks would start with a scintillating scotoma in the right homonymous fields of vision, which lasted for about 10 minutes and was then followed by a bifrontal headache. This was never very severe and lasted no longer than half an hour. Only once or twice had vomiting occurred in the attacks.

In June, 1948, she had two attacks of teichopsia—flashes, spots, zigzag formations—in the right eye only. The first lasted 10 minutes, the second half an hour, but neither attack was followed by headache.

On September 21 at 11 a.m. she suddenly developed a dazzling sensation with spots and flashes of light all over the right visual field. Within a minute a patch of blackness appeared in the upper nasal quadrant of the right field. The dazzling sensation lasted until 4 p.m. and then disappeared, but the blackness remained and obscured vision in this quadrant. No headache followed the attack. She was first seen a month after this episode. In the interval there had been no subjective change in the visual defect in the right eye.

Examination.—Abnormalities were confined to the right eye. In the fundus the retinal arteries were all quite distinctly thinner than in the left eye. The inferior temporal vessel was particularly narrowed, being threadlike in appearance and showing no light reflex. The retinal veins were normal. The disk itself was normal, except for the inferior temporal sector, which was paler than the rest. The retina adjacent to the disk at this point was slightly swollen and blood-streaked. Visual acuity: 6/6 J1 right and left. The right field of vision (Fig. 3) showed a defect in the upper nasal quadrant extending a little into the upper temporal quadrant and corresponding to the occlusion of the inferior temporal artery. The cardiovascular system was normal, and the blood pressure 135/80. The blood Wassermann reaction was negative.

She was seen again two months later, in December. She had had no further attacks of migraine. The right field of vision had improved a little, though she was still blind in the upper nasal quadrant. The fundal appearances were unchanged, except that the retinal oedema had now disappeared.

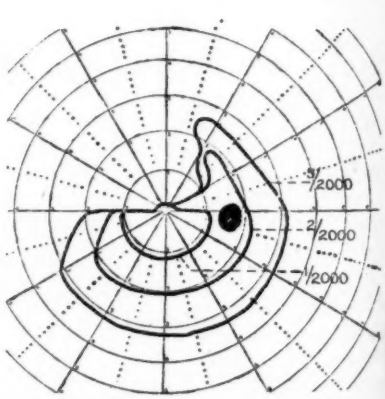


FIG. 3.—Case 2. Field of vision right eye, October, 1948: showing a defect in the upper nasal quadrant and the adjoining part of the upper temporal quadrant.

Case 3

A woman aged 31 was first seen in 1942, when she was 24 years of age. Three years previously, while washing her face one morning, she suddenly lost the sight of her right eye. There was no accompanying headache or ocular pain. For three or four hours the blindness was complete, and then vision returned in the upper half of the field, so that she was left with an inferior altitudinal hemianopia. She was then otherwise symptom-free for about six months. Thereafter, however, she began to suffer from attacks of blurring of vision in the remaining superior half-field associated with ocular pain. These attacks have occurred at intervals of about three months ever since. They begin with a sudden stab of pain over the right eye, which is followed by a sharp pain in the eyeball lasting several minutes. At the same time vision in the lower half-field becomes blurred and remains so for about three hours. There is no family history of migraine.

Examination.—In 1942 the only abnormalities were in the right eye. The field of vision showed an incomplete inferior altitudinal hemianopia with macular sparing (Fig. 4). The superior temporal and nasal retinal arteries were much smaller than the inferior vessels in this eye. In 1948 there was no change in the field defect in the right eye or in the calibre of the affected vessels. Her right disk showed an optic atrophy limited to the superior half of the nerve-head. Visual acuity was 6/5 J1 in the right eye. Neurological examination was otherwise normal. Her blood pressure was 110/75, and the heart and peripheral arteries were normal. The blood Wassermann reaction was negative.

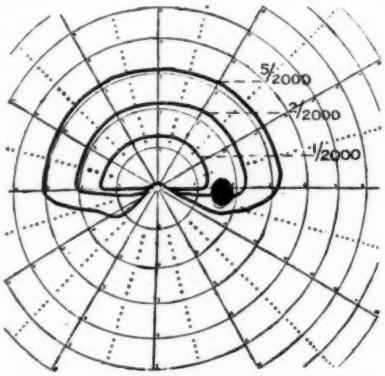


FIG. 4.—Case 3. Field of vision right eye, March, 1942: showing an inferior altitudinal hemianopia.

Case 4

A girl aged 16 was first seen in May, 1948. Between two and three years previously she had had two or three attacks of sudden transient blurring of vision in the left eye, each lasting no longer than a minute and not followed by headache. Then in June, 1946, she developed an influenza-like illness with coryza, generalized aches and pains, malaise, and fever. She went to bed, and after two days felt normal again. On the third day, while lying in bed on her right side, she suddenly saw "black clots" in the left field of vision. Within seconds she became blind in the eye except for a little blurred vision in a small central area (imperfect macular vision). No headache followed this attack of blindness, which has since persisted unchanged.

A year later she began to experience right-sided headaches. She would get pain of a throbbing type over the right brow which came on quite abruptly and lasted up to 20 minutes. At first the headaches were frequent—several times a week—and came on whenever she did a good deal of close work—e.g., reading or sewing. Latterly she had avoided these activities, with a corresponding reduction in the number of her attacks.

On two occasions, in August and September, 1947, she had attacks of scintillating scotoma in the right eye. In the first she suddenly developed a bright dazzling light covering the centre of the right field of vision. After a few minutes this broke up and expanded peripherally, leaving the centre clear, and finally disappeared from the periphery after about 10 minutes. No headache followed. The second attack was very similar but of shorter duration, and again was not followed by headache. There is no family history of migraine.

Examination.—Vision in the left eye was reduced to 6/36 J18. The optic disk was small and atrophic. The retinal arteries were all thin and did not reflect light. The macular area was normal in appearance. The changes were those of an occlusion of the central artery of the retina. The left field of vision was restricted to a small area around the fixation point (tubular vision). The left pupil did not react to direct light, whilst the right pupil failed to react consensually. The right eye was otherwise normal—visual acuity 6/5 J1. There were no other neurological abnormalities, and the cardiovascular system was normal. Her blood pressure was 135/85. The blood Wassermann reaction was negative.

Discussion

The evidence available from both clinical and experimental observation suggests that the symptoms of migraine result from alterations in the calibre of blood vessels in the head, and that both intracranial and extracranial vessels take part in this process. In a fully developed attack two stages are recognized: (1) the stage of pre-headache symptoms—e.g., visual disturbances, paraesthesiae, asphasia—which are thought to be due to functional disturbances of cortical cells secondary to the anoxaemia produced by intracranial angiospasm; and (2) the stage of headache produced by an excessive dilatation, particularly of extracranial arteries, which stimulates the pain nerve endings accompanying these vessels.

Although a vascular theory of migraine was first propounded as long ago as 1870 by du Bois Raymond, it is only in the last decade or so that adequate proof of its occurrence has been obtained. This has been largely due to the work of Wolff and his collaborators, excellently summarized in a recent publication (Wolff, 1948). Their experiments have shown quite clearly that the intensity of the migraine headache is proportional to the degree of dilatation of extracranial arteries, and that the relief from headache achieved by drugs such as ergotamine tartrate is directly related to the degree of vasoconstriction produced.

Whilst the mechanism of headache production is now no longer in doubt, evidence that the prodromal symptoms are the result of intracranial vasospasm has largely been indirect. There are numerous records of patients who have been left with a permanent homonymous visual-field defect after a migrainous attack. A recent case has been described by Rich (1948), and references to previous cases are given in his article. It has been assumed that in such patients arterial spasm has been so intense as to lead to thrombosis and subsequent cerebral softening. Where pathological proof is lacking, however, criticism may be made that such defects may be caused by an underlying vascular abnormality—e.g., an aneurysm or angioma—and that the migraine is of a "symptomatic" rather than a "primary" type. An instructive example of this is mentioned by Kinnier Wilson (1940)—that of a man of 45, a "life-long martyr to migraine," who for 20 years had had a fixed homonymous quadrantanopia, ultimately proved to be caused by a blood-vessel tumour. Adie (1930) described eight cases of permanent hemianopia following migraine attacks. Seven occurred in men—an unusually high proportion for primary migraine. One had had an attack of subarachnoid haemorrhage, which strongly suggests the existence of a structural vascular abnormality.

Evidence of the existence of vasospasm has been accumulated in other ways. James (1945) has shown that a vasodilator drug (carbachol), given regularly, is effective in reducing the frequency of attacks. Wolff in one case was able to show that the inhalation of amyl nitrite, in sufficiently low concentration to produce vasodilatation without a fall in blood pressure, would cause the disappearance of a scintillating scotoma, whereas the latter increased in size when the concentration was great enough to produce hypotension.

That these vascular changes probably produce their effects on the cerebral cortex is shown by the electroencephalographic findings of Engel, Ferris, and Romano (1945). They found that the development of hemianopic teichopsia was accompanied by alterations in the wave pattern from the posterior part of the contralateral hemisphere. In five cases examined during the initial phase of an attack slow irregular 5–7 c/s waves were recorded whilst the visual phenomena lasted and for a brief period afterwards.

Proof of the occurrence of vasospasm in the early stages of a migraine attack is therefore largely circumstantial. The occasional development of retinal arterial occlusion, however, offers more direct and visible evidence, for it seems altogether probable that such thrombosis is secondary to spasm of the affected vessel. Very few such cases have been published.

Galezowski (1882) was probably the first to record such an occurrence. He described four patients afflicted with migraine in each of whom uniocular loss of vision had occurred in relation to attacks of headache. In two, thrombosis of the central artery of the retina was found, one developed an occlusion of the superior branch, whilst the fourth showed peripheral retinal arterial thrombosis with fundal haemorrhages. Their ages ranged from 15 to 67.

Löhlein (1922) described the case of a man who had suffered from attacks of migraine since the age of 20. At the age of 37 he had a nocturnal attack of headache and vomiting; the following morning there was blindness in the left eye. Vision was reduced to the recognition of hand movements in a small peripheral portion of the field and showed no subsequent improvement. Optic atrophy developed, and the condition was considered to be due to a haemorrhage into the optic nerve. Five years later, at the age of 42, a similar attack was followed by blindness in the right eye due to extensive retinal and vitreous haemorrhage, vision later improving. At the age of 46 another attack occurred, reported by Wegner (1926), which resulted in complete blindness and total optic atrophy in the right eye. It seems probable that an occlusion of the central artery of the retina, secondary to vasospasm, was the underlying mechanism of these attacks. Retinal haemorrhage in migraine has also been recorded by Brasch and Levinsohn (1898) and by Vallery-Radot *et al.* (1937), and was seen to a slight extent in Case 2.

Hunt (1915) reported the case of a woman of 31 who had suffered from attacks of migraine since childhood. After a nocturnal attack she noticed a blurring of vision in the right eye and on examination was found to have a central scotoma and some oedema of the nerve-head. These changes regressed and after a period of two months central vision had returned to normal, although a slight pallor of the disk was present. Hunt described the condition as a retrobulbar neuritis and visualized the cause as a vascular lesion in the optic nerve.

The best-documented case is that of Grönvall (1938). His patient was a girl who had begun to suffer from attacks of scotomata and, occasionally, giddiness followed by headache, at the age of 12. At the age of 18 she developed a sudden giddiness associated with a sensation of spots before the eyes. Within a few minutes she became totally blind in the right eye. After a further ten minutes vision returned to the lower half-field of vision, but the upper half remained greyish-black. When examined the following day there was an area of retinal oedema between the disk and the macula; the inferior temporal retinal artery was occluded, and perimetry revealed a defect in the upper nasal quadrant and an adjoining portion of the upper temporal quadrant of the field of vision. The oedema subsided after a month and the field defect showed a slight improvement, but the arterial occlusion remained permanent.

Walsh (1947) records brief details of several patients who suffered from transient attacks of unilateral and bilateral blindness which were sometimes followed by migrainous headaches. One patient developed permanent occlusion of the central artery of the retina in an attack occurring four days after parturition.

Finally, Grimsdale (1940) has written an interesting description of his own personal experience of an attack of retinal arterial spasm, which resulted in an occlusion of a branch of the superior temporal vessel.

Of these nine recorded cases of retinal arterial obstruction in migraine four have occurred in the central artery of the retina, giving rise to severe uniocular blindness; four occurred in peripheral branches, producing sector field defects; and one (Hunt's case) developed a central scotoma, possibly the result of an occlusion of an intraneural branch of the central retinal artery. In the four cases recorded here, one has involved the central retinal artery and three its peripheral branches.

No age group seems particularly predisposed to these complications; there is certainly no evidence that increasing age and coincident arteriosclerotic changes render the migrainous subject liable to such sequelae, for they have affected young and old alike. In the cases described here there were no signs of local retinal or generalized arterial disease, nor was there evidence of any possible source of emboli. Cases 1 and 2 suffered from attacks of migraine before the onset of the retinal occlusion, whilst in Cases 3 and 4 the occlusion was apparently the first symptom of the disease.

Migraine should therefore be considered as a possible cause of those cases of retinal occlusion, occasionally experienced in practice, in which no cardiovascular disease can be found. The condition is probably less uncommon than its recorded occurrence might suggest. Three of the four cases here described have been seen within a period of 12 months. Their interest lies chiefly in the fact that they provide further evidence that the symptoms of migraine are the result of vasomotor disturbances in the territory of cranial blood vessels.

Summary

Four cases of retinal arterial occlusion occurring in migraine are reported. In one case the central artery of the retina was affected; in three cases occlusion occurred in a single peripheral branch.

Such cases provide evidence for the theory that the pre-headache phenomena of migraine are due to vasospasm.

I wish to thank Dr. F. R. Ferguson for his permission to publish the records of cases under his care.

References

Adie, W. J. (1930). *Lancet*, **2**, 237.
Brasch, M., and Levinsohn, G. (1898). *Berl. klin. Wschr.*, **35**, 1146.
Engel, G. L., Ferris, E. B., jun., and Romano, J. (1945). *Amer. J. med. Sci.*, **209**, 650.
Galezowski, X. (1882). *Lancet*, **1**, 176.
Grimsdale, H. (1940). *Brit. J. Ophthal.*, **24**, 208.
Grönvall, H. (1938). *Acta ophthal., Kbh.*, **16**, 602.
Hunt, J. R. (1915). *Amer. J. med. Sci.*, **150**, 313.
James, A. K. (1945). *British Medical Journal*, **1**, 663.
Löhlein, W. (1922). *Dtsch. med. Wschr.*, **48**, 1408.
Rich, W. M. (1948). *British Medical Journal*, **1**, 592.
Vallery-Radot, P., Blamoutier, P., Mawas, L., and Hamburger, J. (1937). *Ann. Méd.*, **42**, 132.
Walsh, F. B. (1947). *Clinical Neuro-Ophthalmology*. Williams and Wilkins, Baltimore.
Wegner, W. (1926). *Klin. Mbl. Augenheilk.*, **76**, 194.
Wilson, S. A. K. (1940). *Neurology*. Arnold, London.
Wolff, H. G. (1948). *Headache and Other Head Pain*. Oxford University Press, New York.

STUDIES IN PRIMARY PLEURISY WITH EFFUSION*

BY

BRIAN C. THOMPSON, M.D.

(From the Tuberculosis Service, Otago Hospital Board, New Zealand)

This paper is on the subject of primary pleurisy with effusion and is not concerned with effusions arising in patients with established pulmonary tuberculosis. The pathogenesis of such cases is not difficult to imagine, though it is a curious fact that so many occur in patients with old-standing, often calcified, and apparently inactive pulmonary lesions, and that the prognosis is remarkably good (Thompson, 1947a). These can properly be called "secondary" tuberculous pleural effusions. The fluid which may form in the course of artificial-pneumothorax treatment is perhaps a special case in this group.

The "primary" effusion of my definition formed the subject of a previous investigation in which 190 cases were studied over a period of years, with follow-up results which were virtually complete, including regular routine radiography of the chest (Thompson, 1946, 1947b). Although by definition coexisting or preceding pulmonary tuberculosis was not present in this earlier series of cases, radiographs sometimes revealed lesions within the thorax that were typical of the tuberculous primary complex of Ghon. These lesions were characterized by enlargement of the hilar lymph glands, or by parenchymal infiltration, or by both together, sometimes including evidence of bronchial stenosis or atelectasis of a broncho-pulmonary segment. Where a parenchymal lesion was apparently alone, this was of the primary-infection type in which the glandular component could reasonably be regarded as radiologically invisible. These intrathoracic lesions were known sometimes to have preceded the pleural effusion; in no case did the effusion come first. In some cases the effusion occurred on the same side as the pulmo-glandular complex; in others it occurred on the opposite side.

Follow-up showed that 25% of all cases developed tuberculosis within five years. The earliest evidence of this subsequent disease often occurred within a few months, soon enough to indicate that it was directly associated with the preceding pleural effusion, and that it was not, for example, a further tuberculous infection from an outside source. In nearly one-half of the cases of subsequent tuberculosis, this became evident within the first year of observation. Two-thirds of the remainder occurred within the second year. None occurred later than the fifth year. The incidence, course, and prognosis of the subsequent tuberculosis was not apparently related to the age of the patient or his social state, or to such clinical conditions as the magnitude of the effusion, the degree of toxaemia, or the presence of demonstrable intrathoracic primary lesions. Nor, contrary to the opinion of Trudeau (1939), was there evidence that any treatment, or absence of treatment, of the original condition influenced the ultimate course of the disease.

Since the publication of the above studies, opportunity has arisen for observing the development of pleurisy with effusion from its earliest beginnings in persons already under observation, especially among nurses and medical students at Dunedin Hospital, who undergo regular tuberculin testing and *x*-ray examination as part of their routine medical care. The following selected case histories are presented as clinical illustrations of some of the factors involved.

*Paper read at a meeting of the Royal Australasian College of Physicians in Dunedin on September 8, 1948.

Case Reports

Case 1.—A student nurse aged 28 was negative to intradermal injection of tuberculin P.P.D. first and second strength on entry in March, 1946, and again in June. At her next routine examination in January, 1947, she gave a 4-plus reaction to P.P.D. first strength, and a radiograph showed involvement of the left lung and tracheo-bronchial glands typical of primary tuberculosis. Though well and without symptoms, she had evidently incurred a recent primary infection, probably a few weeks previously, when she had complained of a transient malaise and sore throat, but without reporting sick. After a month's leave at home she returned to duty. In July an acute left pleurisy with effusion supervened.

Comment.—This is a case of typical primary tuberculous infection in a previously uninfected adult with an intrathoracic primary complex, followed by pleural effusion on the same side six months later. Such an interval is regarded as about the average duration between the entry of tubercle bacilli and the development of pleurisy, but there are wide variations. Delay for a longer period is easily explained by the traditional latency of tuberculosis. The shortest period I have seen was in Case 2.

Case 2.—A student nurse aged 19 was negative to both strengths of P.P.D. on entry in September, 1945, and again in June, 1946. Sixteen weeks later she developed an acute left-sided pleurisy with lymphocytic effusion. Three weeks after that an effusion also occurred on the right side.

Comment.—A pleural effusion occurred four months after a negative tuberculin test and therefore not more than 10 weeks from the latest possible date of conversion to tuberculin-positivity, according to the accepted incubation period of about six weeks following primary infection (Wallgren, 1945). The subsequent contralateral pleurisy also occurred with unusual rapidity, and with no indication of its causation. The patient made an uneventful recovery and eventually returned to duty.

Case 3.—A nurse aged 18 on entry in 1942 was Mantoux-negative at that time and was repeatedly negative up to January, 1946, when she was found to be negative to the first strength of P.P.D. but positive to the second strength. The chest radiograph was clear. In September, 1946, she developed cough and pain in the left side. A pleural friction-rub was heard in the left axilla, corresponding to *x*-ray evidence of a pulmonary lesion of primary type, and the E.S.R. was 18 mm. Four months later a pleural effusion occurred on the opposite side.

Comment.—Pleural effusion developed contralateral to a primary tuberculous pulmonary lesion, over which dry pleurisy had been noted but which had not led to the formation of fluid. As in Case 3 there was nothing to suggest a haematogenous spread of disease. The passage of infection from the left to the right hemithorax could, however, have been by way of the mediastinal lymph glands.

Case 4.—A student nurse aged 23 was Mantoux-negative on entry in 1944. In January, 1946, she was still negative to both strengths of P.P.D., but 12 weeks later the sites of both these intradermal injections became acutely inflamed. A radiograph showed enlargement of glands in the left hilum (Fig. 1). She developed an irritative cough towards the end of the year, and in March, 1947, was found to have an accumulation of fluid between the upper and lower lobes of the left lung (Fig. 2), which was aspirated and replaced by air. Though no pulmonary lesion could be seen, she had a productive cough with tubercle bacilli in the sputum, and in view of a localized wheezing

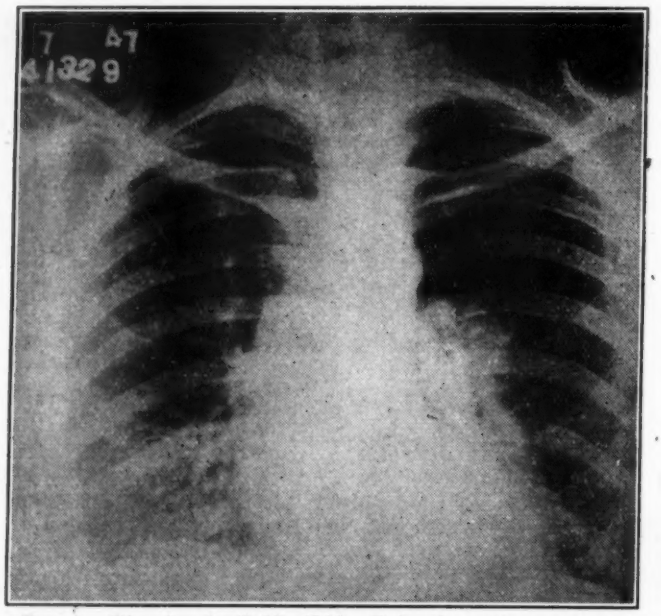


Fig. 1.—Case 4. April 30, 1946. Delayed positive reaction to Mantoux tests done 12 weeks previously. Left pleural effusion occurred 10 months later.

respiration it was suspected that the caseous gland mass had broken through into the bronchial tract. This was confirmed by bronchoscopy, which revealed an ulcerated area on the anterior aspect of the left main bronchus, just proximal to its upper division. After prolonged sanatorium treatment, during which she became entirely free from symptoms and from recoverable tubercle bacilli, she developed an acute pleural effusion on the right side, just 24 months from first becoming tuberculin-sensitive.

Comment.—The phenomenon of delayed reaction to tuberculin retained in the skin through the period of primary infection (Daniels, 1943) enables the date of that infection to be fixed very exactly. This nurse must have received her first dose of tubercle bacilli in the second fortnight of February, 1946, her left-sided effusion appearing 12 months later, with persistence of the glandular component of the primary complex throughout that period. It may be significant that the fluid spread from the hilum in the interlobar fissure without extending widely over the costal surface, which it was quite free to do, as the subsequent artificial pneumothorax showed (Fig. 3). The mass of caseous glands radiologically seen at the hilum were found to press on and to erode the adjacent bronchus. It is reasonable to suppose that these same glands could similarly involve the pleural sac, lying as they do against its hilar reflection, and that extension to other lymph glands in the mediastinum could reach the opposite pleura, producing there the later effusion.

Fig. 2.—Case 4. March 8, 1947. Lateral view showing fluid lying in the interlobar fissure.

Case 5.—A medical student aged 22 was Mantoux-negative up to his final year, when he incurred a brief febrile illness with cough and chest pain. A radiograph showed a left-sided primary tuberculous complex. Ten months later an effusion developed on the same side, associated with very severe toxic disturbance. Despite repeated aspiration the fluid always re-formed rapidly. His temperature remained high and he gradually declined into an almost typhoid state. Impaired percussion and bronchial breathing were found to the right of the sternum, and a small effusion eventually formed in the right pleural cavity. The clinical picture and *x*-ray appearances suggested the presence of so large a caseous gland mass as to constitute a tuberculous mediastinitis, with pressure atelectasis of the right lung base. After air-replacement of the left-sided effusion, a thoracoscope was introduced. There were no tubercles to be seen, but the pleura was intensely pink, and fine filamentous adhesions, easily separable, were forming between the upper lobe of the lung and the parietal pleura. Parenteral streptomycin was begun, 0.5 g. twice daily, with immediate and dramatic results. Within two days his temperature fell to normal, his appetite returned, apathy abated, and recovery steadily advanced to convalescence.

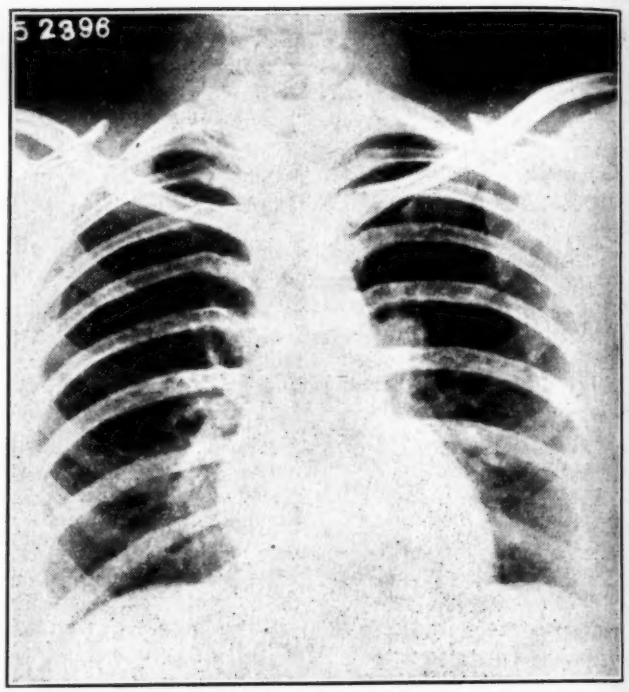


Fig. 3.—Case 4. July 3, 1947, after aspiration of fluid and replacement by air. A free pneumothorax is present, with some displacement of the heart to the right.

Comment.—The pleural effusion followed a primary tuberculous complex on the same side, and spread to the other side apparently by way of the mediastinum. Miliary

disease was excluded by thoracoscopy. Striking features were the unusual degree of toxaemia, so great that a fatal issue looked likely, and the prompt response to streptomycin.

Case 6.—A woman doctor aged 24 was Mantoux-negative throughout her training, and up to December, 1947, when for some weeks she experienced vague malaise, culminating in an outbreak of erythema nodosum. A radiograph showed a lesion in the right upper lung field typical of primary tuberculosis. On strict rest in bed her temperature fell from 100° F. (37.8° C.) to normal and her E.S.R. from 25 to 6 mm., and her general condition rapidly improved. Her only symptom occurred 16 weeks from the onset of the skin eruption—a transient pain beneath the right scapula aggravated by deep inspiration. There were no physical signs, but a radiograph showed a slight peripheral spread of the earlier lung lesion, with definite pleural reaction.

Comment.—The primary infection was marked by the occurrence of erythema nodosum. Pleurisy ensued on the same side as the primary lesion, clearly as a result of local spread from its pulmonary component. There was no constitutional upset and no rise of temperature, while the E.S.R. remained well within normal limits during this latter episode.

Case 7.—A schoolgirl aged 15 was examined as a contact of her father, who had recently died from acute pulmonary tuberculosis. She was found to have an active primary complex on the right, with contiguous bronchopneumonic spread from the focus in the lower lobe. This localized extension increased under conditions of strict rest in bed, and eight weeks later a right pleural effusion supervened. Thereafter she showed steady clinical improvement and was discharged from sanatorium 12 months later, in excellent condition, to live quietly on the family farm. Within a month there appeared below the left clavicle a new infiltration which spread slowly, to become arrested and show signs of regression only after 18 months of observation. Throughout this period, from the initial resolution of her effusion, she was entirely without symptoms, gained weight, and had a normal unchanging sedimentation rate. There was, however, radiological evidence of the glandular component of the primary complex persisting right up to the development of the subclavicular infiltration and resolving only when the latter reached apparent stability.

Comment.—This case is a further example of pleural effusion following a recent primary complex, which remained incompletely resolved during medical treatment and gave only radiological evidence of its existence, and subsequently led to pulmonary tuberculosis on the opposite side.

Discussion

These cases have been chosen for the light they throw on the pathogenesis of pleural effusion. All had undergone a recent primary tuberculous infection and were under close observation before and after that event. In six of the seven cases a primary complex within the thorax was seen to develop which was radiologically visible throughout the pleurisy in five. Case 7 is an example of the development of subsequent pulmonary tuberculosis, and the primary complex continued to be visible by radiograph.

One way in which the pleura may be invaded from the primary complex is illustrated by Cases 6 and 7, in which direct spread from the pulmonary focus was observed. Another way is shown in Cases 3, 4, and 5, in which there was strong evidence that the lymphatic gland component eroded the pleura near its mediastinal reflection. The opposite pleura was subsequently affected in three cases (Nos. 2, 4, and 5), indicating that so-called bilateral effusions are due probably to spread from adjacent lymph glands.

The latent period between primary infection and exudative pleurisy may be as short as 16 weeks (Case 2) but is usually between 6 and 12 months. Persistence of evidence of an active primary complex should lead one to expect pleurisy in any case of recent tuberculous infection. The term "primary" pleurisy with effusion is therefore used definitively, to make clear this association, though in a strict pathological sense it doubtless belongs to the indeterminate post-primary phase. More distinctly post-primary is the relatively uncommon pleural effusion, usually bilateral, which may accompany generalized haematogenous dissemination from the primary complex, with miliary tuberculosis throughout the lungs, extrapulmonary lesions, and even polyserositis.

It seems that caseous lymph glands behave in the mediastinum in a manner similar to that often observed in the neck, as Erwin (1944) has suggested, by breaking through the boundary of least resistance. This may be the wall of a bronchus, clinically not uncommon, as in Case 4. It is reasonable to suppose that the contiguous pleura may be invaded in the same way, though Burke (1940) has advanced the possibility of retrograde spread by way of the subpleural lymphatics. Tubercle bacilli can nearly always be grown from the exudate by careful technique (Close, 1946), and one cannot doubt that they are directly concerned.

All these cases were in young adults. Pleurisy with effusion does of course occur in children, but very infrequently compared with the large number of primary tuberculous infections that occur during childhood (Hardy and Kendig, 1945). As children also do not tend to develop progressive pulmonary tuberculosis, it may be supposed that they are better able to resist such infections before puberty than after puberty, and to arrest the primary lesion usually at a stage short of pleural involvement.

This study offers no further evidence on the pathogenesis of subsequent tuberculosis. Case 7 illustrates the close succession of events—from primary lesion, through exudative pleurisy, to pulmonary infiltration—and the likelihood that the whole process is largely beyond the influence of our present therapeutic means.

Conclusions

Primary pleurisy with effusion is an incident in the natural history of tuberculosis. It arises by direct pleural involvement from either the pulmonary or the glandular component of an active intrathoracic primary complex, incurred as a rule a few months previously. Specially susceptible to this condition are adolescents and young adults who, having escaped the tubercle bacillus earlier in life, meet it for the first time by casual contact, usually outside the home.

The subsequent course is probably not different from that seen in other forms of late primary infection, with a marked tendency to pass into a stage of chronic pulmonary or extrapulmonary tuberculosis. Such progression may be entirely subclinical and may take place irrespective of or even during medical treatment.

The pleural effusion is to be regarded less as a disease in itself than as significant of persistent and dangerous primary tuberculosis.

References

Burke, H. E. (1940). *J. thorac. Surg.*, **9**, 506.
Close, H. G. (1946). *Lancet*, **1**, 193.
Daniels, M. (1943). Ibid., **2**, 600.
Erwin, G. S. (1944). *Tubercle*, **25**, 44.
Hardy, J. B., and Kendig, E. L. (1945). *J. Pediat.*, **26**, 138.
Thompson, B. C. (1946). *Amer. Rev. Tuberc.*, **54**, 349.
—— (1947a). *Tubercle*, **28**, 229.
—— (1947b). *British Medical Journal*, **1**, 487.
Trudeau, F. B. (1939). *Amer. Rev. Tuberc.*, **39**, 57.
Wallgren, A. (1945). *Amer. J. Dis. Child.*, **70**, 263.

AETIOLOGY OF ERYTHEMA NODOSUM IN CHILDREN

BY

S. A. DOXIADIS, M.D.

Lecturer in Child Health, University of Sheffield

Erythema nodosum is considered by most authors to be a non-specific manifestation of hypersensitivity to various allergens, mainly bacterial (Collis, 1933; Rötnes, 1936; Spink, 1937; Wallgren, 1938a; Ernberg and Gabinus, 1939; Perry, 1944; Skiöld, 1945; Löfgren, 1946), although some still consider it to be a specific infectious disease (Miescher, 1948).

Of the infective agents responsible for the hypersensitivity, *Mycobacterium tuberculosis* is the commonest in childhood. Second in frequency is the streptococcus, the aetiological significance of which has been demonstrated by Collis (1932). Very few cases in childhood are due to hypersensitivity to other organisms. An exception to this is found in the parts of the U.S.A. where coccidioidomycosis is common, for about 11% of the children with this infection have an eruption similar to erythema nodosum (Smith *et al.*, 1946).

The relation of erythema nodosum to tuberculosis in children was noticed as long ago as 1872 (Uffelmann, 1872) but little attention was given to it until Ernberg (1921) published his theory and observations on the nature of this relation. The opinion that erythema nodosum is commonly a manifestation of primary tuberculous infection became accepted more generally as a result of the work of Wallgren (1927, 1928, 1930, 1931). Of 800 children with erythema nodosum whom he had seen by 1938 (Wallgren, 1938a) 95% had a positive tuberculin reaction. Reports on the tuberculin reaction of children with erythema nodosum have been published by many authors on the Continent (Göbel, 1933; Moro, 1934; Landorf, 1935; Debré *et al.*, 1938; Mallet, 1938; Nobécourt and Briskas, 1941; and many others).

Although it is known (Wallgren, 1938a) that the incidence of tuberculous infection in children with erythema nodosum varies from country to country, studies in the British Isles (Boganovitch, 1930; Begg, 1932; Collis, 1933; Forman and Whitwell, 1934; Thompson, 1939; Gray, 1945) and North America (Dickey, 1932; Brandon *et al.*, 1938; Lincoln *et al.*, 1944; Roddy, 1949) have been based on small series of cases only. The single exception is the study by Perry (1944), who determined the incidence of tuberculosis in 112 patients with erythema nodosum. Sixty-seven were children—in 29 (43.3%) the eruption was definitely related to tuberculosis, in 21 (31.3%) the relation was probable, and in 17 (25.4%) tuberculous infection was excluded.

The present paper concerns 100 children with erythema nodosum. It is presented because of the small number of similar observations in this country and in order to draw the attention of family doctors once more to the importance of recognizing erythema nodosum in children as a valuable sign of tuberculous infection.

Material

All the 100 children were seen and investigated in the Children's Department of the Royal Victoria Infirmary, Newcastle-upon-Tyne, or at the Children's Hospital, Sheffield. Seventy were seen by the author and the information for the remaining 30 was obtained from their case notes. In 20 children a course of sulphonamides preceded the eruption by a period varying from 12 hours to 12 days. These children are included in the present series, as it is considered (Löfgren, 1945; Doxiadis and McLean, 1948) that erythema nodosum occurring after the administration of sulphonamides is fundamentally the same as that in which the eruption is spontaneous.

The age and sex incidence is shown in Table I. The low incidence after the age of 13 is without significance because older children receive treatment in other departments.

TABLE I.—*Age and Sex Incidence of Erythema Nodosum*

Age, Years Completed	No. of Children	Age, Years Completed	No. of Children
1	6	8	7
2	5	9	11
3	6	10	13
4	5	11	7
5	4	12	10
6	6	13	11
7	7	14	2

Boys 38. Girls 62.

The seasonal incidence is presented in Table II, and it can be seen that there is a smaller number of cases in summer and autumn.

TABLE II.—*Seasonal Incidence of Erythema Nodosum*

Month	No. of Children	Month	No. of Children
January	12	July	3
February	10	August	6
March	10	September	5
April	9	October	6
May	11	November	10
June	5	December	13

Results

All children were tested with tuberculin. The first test was either the application of tuberculin jelly on the skin or the intradermal injection of 0.01 mg. or less (0.005–0.01 mg.) of old tuberculin. If the test was positive no further tests were performed. If the reaction was negative then larger amounts of old tuberculin (0.1–1 mg.) were injected intradermally.

A positive reaction to tuberculin was found in 88 children (88%). In three of these the first test was negative or doubtful and all three showed a strongly positive reaction to 0.1 mg. of tuberculin. Of the 12 tuberculin-negative children, four were tested with 0.1 mg. and eight with 1 mg. or more of old tuberculin.

Of the 88 tuberculin-positive children, 59 (67%) had other evidence of active tuberculous infection. In 54 the radiograph showed marked undoubted unilateral enlargement of the hilar shadows, and in some of these there were opacities in the lung, on the same side as the hilar enlargement, consistent with the diagnosis of primary tuberculosis. Five children had cervical adenitis and in three the pus obtained by incision or aspiration contained *Myco. tuberculosis*.

Within three months after the appearance of erythema nodosum a pleural effusion developed in four of those children, there was an extension of the radiological signs in the lungs in two, miliary tuberculosis developed in one, and one child died from tuberculous meningitis.

Of the remaining 29 tuberculin-positive children, there were no radiological changes in 22, and doubtful changes in seven.

The relation of tuberculous infection to erythema nodosum is summarized in Table III. No further investi-

TABLE III.—*Relation of Erythema Nodosum to Tuberculous Infection*

Tuberculin-positive children	88
With other evidence of active primary tuberculous infection	59
Without or with doubtful other evidence of active primary tuberculous infection	29
Tuberculin-negative children	12
Total:	100

gations were made in the 12 tuberculin-negative children. The eruption followed a sore throat in five of them and scarlet fever in one.

In none of the 100 children was there any evidence of rheumatic infection, and in the 80 who were observed for at least six months after the eruption there has been no sign of involvement of the heart.

Discussion

The high incidence (88%) of positive tuberculin reactions in the 100 children with erythema nodosum is comparable to the incidence found by many Continental workers and is even higher than that in the only other recent series from this country (Perry, 1944).

It cannot be stated with certainty that the erythema nodosum was due to tuberculosis in all the 88 tuberculin-positive children. It may be said, however, that at least in the 59 (67%) who at the time of the eruption had other evidence of active tuberculous infection there was a close relation between the eruption and the infection. In the remaining 29 children (33%) the same relation probably existed.

These results show that in this country, too, most of the children with erythema nodosum are passing through their primary tuberculous infection. Any child therefore with erythema nodosum should be considered to have been recently infected with tuberculosis unless carefully performed tuberculin tests are negative. Because of the high degree of sensitivity to tuberculin of the tuberculin-positive children with erythema nodosum a jelly test is usually sufficient to elicit a positive reaction. If intradermal tests are used, the amount of old tuberculin in the first injection should never exceed 0.01 mg.

Special investigations were not made in the 12 tuberculin-negative children, and there is therefore no direct evidence that a streptococcal infection was the main aetiological factor, though a sore throat or scarlet fever preceded the eruption in six.

The absence of any demonstrable relation between erythema nodosum and rheumatic fever in the present series is worthy of emphasis. Some doctors still consider that erythema nodosum is "rheumatic" in origin and fail therefore to carry out any further investigations. Out of 800 children with erythema nodosum Wallgren (1938b) saw only one in whom the eruption was related to rheumatic fever. Löfgren (1946), in his study of 184 cases of erythema nodosum in adults, found that there was no evidence that erythema nodosum is connected with rheumatic fever; and Skiöld found a probable connexion in only five (1.4%) out of 354 adults with erythema nodosum. It is clear, therefore, that erythema nodosum is very rarely due to rheumatic fever.

Summary

Out of 100 children with erythema nodosum 88 had positive tuberculin reactions. In 59 of these there was an active primary tuberculous lesion. In the remaining 29 tuberculosis was probably the aetiological factor. In none of the children was there any connexion between erythema nodosum and rheumatic fever.

I wish to thank Professor J. C. Spence, Professor E. J. Wayne, and Dr. T. Colver for their permission to make use of their cases, Professor R. S. Illingworth for his valuable advice, and Dr. D. Stone for his assistance. Part of the material was collected during the tenure of a Luccock Research Fellowship at the Medical School, King's College, University of Durham.

REFERENCES

Begg, N. D. (1932). *Brit. J. Child. Dis.*, **29**, 193.
Boganovitch, V. (1930). *Arch. Dis. Childh.*, **5**, 56.
Brandon, K. F., Hardman, R. P., and Birke, W. H. (1938). *Canad. publ. Hlth J.*, **29**, 533.
Collis, W. R. F. (1932). *Quart. J. Med.*, **1**, 141.
—— (1933). *British Medical Journal*, **2**, 1162.
Debré, R., Saenz, A., Broca, R., and Mallet, R. (1938). *Rev. franç. Pédiat.*, **14**, 433.
Dickey, L. B. (1932). *Amer. Rev. Tuberc.*, **26**, 614.
Doxiadis, S. A., and McLean, D. (1948). *Arch. Dis. Childh.*, **23**, 273.
Ernberg, H. (1921). *Jahrb. Kinderheilk.*, **45**, 1.
—— and Gabinus, O. (1939). *Amer. J. Dis. Child.*, **57**, 1012.
Forman, L., and Whitwell, G. P. B. (1934). *Guy's Hosp. Rep.*, **84**, 213.
Göbel, W. (1933). *Z. Kinderheilk.*, **55**, 30.
Gray, W. D. (1945). *British Medical Journal*, **2**, 286.
Landorf, N. (1935). *Acta paediatr., Stockh.*, **17**, suppl. 1, 180.
Lincoln, E. M., Alterman, J., and Bakst, H. (1944). *J. Pediat.*, **25**, 311.
Löfgren, S. (1945). *Acta med. scand.*, **122**, 175.
—— (1946). Ibid., suppl. 174.
Mallet, R. (1938). *Erythème Noueux et Infection Tuberculeuse.* Thèse No. 187. Paris.
Miescher, G. (1948). *Schweiz. med. Wschr.*, **78**, 269.
Moro, E. (1934). *Derm. Wschr.*, **98**, 633.
Nobécourt, P., and Briskas, S. B. (1941). *Pr. méd.*, **49**, 713.
Perry, C. B. (1944). *British Medical Journal*, **2**, 843.
Roddy, R. L. (1949). *J. Pediat.*, **34**, 338.
Rötnes, P. L. (1936). *Acta derm.-venereol., Stockh.*, **17**, suppl. 3.
Skiöld, N. (1945). *Acta med. scand.*, suppl. 157.
Smith, C. E., Beard, R. R., Whiting, E. G., and Rosenberger, H. G. (1946). *Amer. J. Publ. Hlth*, **36**, 1394.
Spink, W. W. (1937). *Arch. intern. Med.*, **59**, 65.
Thompson, B. C. (1939). *British Medical Journal*, **1**, 159.
Uffelmann, J. (1872). *Dtsch. Arch. klin. Med.*, **10**, 454.
Wallgren, A. (1927). *Z. Kinderheilk.*, **43**, 543.
—— (1928). *Amer. J. Dis. Child.*, **36**, 702.
—— (1930). In Engel and Pirquet's *Handbuch der Kindertuberkulose*, vol. 1, p. 809. Leipzig.
—— (1931). *Amer. J. Dis Child.*, **41**, 816.
—— (1938a). *Lancet*, **1**, 359.
—— (1938b). *Amer. J. Dis. Child.*, **55**, 897.

POST-OPERATIVE THROMBOSIS*

INVESTIGATION OF A PROPOSED TEST FOR ITS PREDICTION

BY

G. W. VAUSE GREIG, M.B., F.R.C.S.

Surgical Registrar, the General Infirmary, Leeds

In a paper on intravascular thrombosis Cummine and Lyons (1948) claimed that by the examination of the post-operative coagulation time and estimation of the plasma fibrinogen-B they could foretell the onset of impending thrombosis. They further suggested that if the coagulation time as measured by the capillary tube method drops to four minutes, and if fibrinogen-B (an intermediate product in the change of fibrinogen into fibrin) can be demonstrated in the blood, then prophylactic anticoagulant therapy should be instituted.

In spite of the introduction of heparin and dicoumarol, thrombosis and embolism still contribute to the incidence of post-operative morbidity and mortality, and a simple test to determine which patients should be given anti-coagulant drugs to prevent these complications is being widely sought. Investigation of a series of cases, using the proposed tests of Cummine and Lyons, was therefore undertaken.

*Being the subject of a short paper delivered before the Surgical Travellers Club at Leeds on January 21, 1949.

Method

It was decided to measure the coagulation time before operation and then daily after operation, but the fibrinogen-B test, which entails a venepuncture, was done pre-operatively, the day after operation, and then subsequently only when there was a fall in the coagulation time.

This regime was followed in 43 cases, and in a further eight acute cases the estimations were started the day after operation. All the patients investigated had undergone a major operation varying from a partial gastrectomy to a prostatectomy. Of the 51 patients 29 were over 55 years of age; only six were under 40, and of these one was a case of cholelithiasis for which a cholecystectomy had been performed, three had had partial gastrectomies for chronic duodenal ulceration, and one (the youngest of the series, aged 32) had had an abdomino-perineal resection for carcinoma of the rectum. Thus all were in the groups in which post-operative thrombosis is most common.

The estimations were discontinued when the patient was ambulant, as it was considered that by that time the danger of spontaneous intravascular clotting has generally passed. That this belief is erroneous was proved by the one case in the series which developed a thrombosis.

Results

The results may be divided into four groups.

Group 1.—In 12 cases the coagulation time throughout was above four minutes and no fibrinogen-B was found in their blood post-operatively (Fig. 1).

Group 2.—Ten patients had fibrinogen-B in their blood post-operatively, but their coagulation time remained higher than four minutes (Fig. 2).

Group 3.—Eleven cases showed a lowering of the coagulation time to four minutes or less but had no fibrinogen-B in their blood at the time of this fall (Fig. 3).

Group 4.—In 18 cases there was a fall of the coagulation time to four minutes or less associated with the finding of fibrinogen-B in the blood.

According to Cummine and Lyons there is no danger of thrombosis in the first three groups, and none of the cases in these groups showed clinical signs suggesting it.

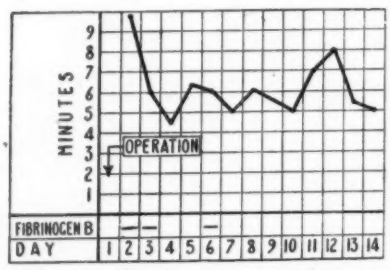


FIG. 1.—Graph of case typical of Group 1 (woman aged 76; gallstone ileus). Coagulation time remaining above four minutes. No fibrinogen-B.

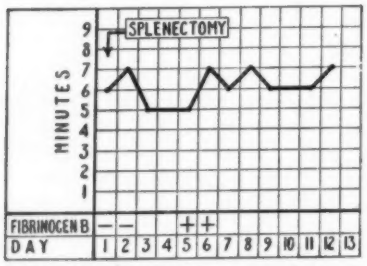


FIG. 2.—Graph of case typical of Group 2 (woman aged 51; portal hypertension). Fibrogen-B present, but no lowering of coagulation time.

The cases in Group 4, comprising more than one-third of the whole series, satisfied the criteria laid down by Cummine and Lyons for the prophylactic administration of heparin and dicoumarol. The first two cases showing this fall in coagulation time coincident with a positive fibrinogen-B test were given heparin and dicoumarol, and in both, as was to be expected, the result was a marked prolongation of the clotting time, but in one the plasma fibrinogen-B persisted (Fig. 4). However, as these two cases occurred among the first five investigated, and as they displayed no evidence of thrombosis, it was decided to withhold anticoagulant drugs until the tests had been more certainly evaluated.

Out of the subsequent 16 cases in Group 4 only one developed a thrombosis, and this took place after the patient was ambulant and the daily coagulation time determination had been discontinued (Fig. 5): the day after the thrombosis her coagulation time was within normal limits and her blood free from fibrinogen-B. This woman, who had a deep femoral thrombosis, was not treated with heparin or dicoumarol, but was kept ambulant, with a firm crêpe bandage from toes to groin. She suffered no embolic phenomena or further spread of the thrombosis, and when seen three months later had only a slight residual swelling of the leg in the ankle region, with no incapacity.

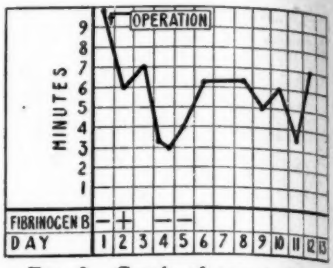


FIG. 3.—Graph of case typical of Group 3 (man aged 58; carcinoma of rectum). Lowering of coagulation time to below four minutes, but not associated with fibrinogen-B in the blood.

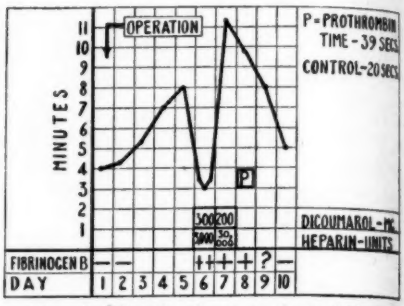


FIG. 4.—Graph of case typical of Group 4 (man aged 57; partial gastrectomy for duodenal ulcer). Coagulation time below four minutes together with fibrinogen-B in the blood.

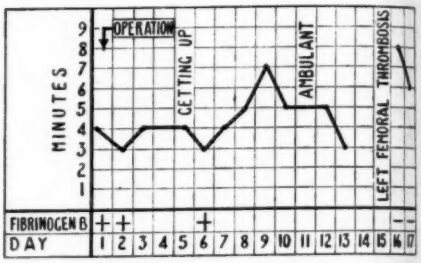


FIG. 5.—Carcinoma of caecum in a woman aged 64. The only case in Group 4 showing clinical signs of thrombosis—occurring after patient was fully ambulant.

Discussion

As this investigation progressed disappointment was felt because these proposed tests did not enable us to predict accurately the cases which would develop post-operative thrombosis: it is obviously not practicable to treat 35% of patients with heparin and dicoumarol. However, one point of interest did arise. This was that of the 43 cases examined both before and after operation 34 showed a fall in the coagulation time in the first twenty-four hours after operation and 21 of these had a fall to four minutes or less. Ten patients whose clotting times were measured at the end of operation before they left the operating theatre all showed a marked increase in rate of coagulation. These results suggest that what Bergquist (1940) called "the pre-thrombotic state" is not infrequently present within the first few hours after operation or even earlier, during operation, and this is the danger time when thrombosis in the leg veins is most likely to begin.

Summary

Investigations were carried out in 51 cases on a proposed method for the prediction of post-operative thrombosis. It was

decided that the results were not accurate enough to warrant the use of heparin and dicoumarol in those cases in which the tests were positive.

It was found that there is commonly a fall in coagulation time during or immediately after operation, and it is suggested that thrombosis, if it does occur, probably starts during this period.

I am indebted to Professor Digby Chamberlain, who proposed and guided these investigations, and on whose cases they were carried out.

References

Bergquist, G. (1940). *Acta chir. scand.*, **83**, 415.
Cummine, H., and Lyons, R. N. (1948). *Brit. J. Surg.*, **35**, 337.

INCIDENCE OF SIGNS USUALLY CONNECTED WITH THYROTOXICOSIS

WITH SPECIAL REFERENCE TO LID LAG*

BY

W. P. U. JACKSON, M.D., M.R.C.P., D.C.H.

Late Assistant Physician, Selly Oak Hospital, Birmingham

During recent observations on the coincidence of hyperthyroidism and peptic ulcer (Jackson and Pinkerton, 1949) it was noticed that a large proportion of patients with the latter complaint showed von Graefe's sign (lid lag), one of the characteristic ocular phenomena of thyrotoxicosis. This sign was first described in 1864 by von Graefe, who said: ". . . namentlich folgt bei Senkung der Cornea das obere Augenlid nicht." He remarked that it was not the result of exophthalmos, as it was present in early cases of thyroid disease which showed no proptosis. He considered it to be a sign pathognomonic of hyperthyroidism in the early stage: " . . . geringen Grade der Krankheit einen pathognomonischen Werth hat." It is now recognized that the sign is not peculiar to thyrotoxicosis (Eason, 1927) and that it may occur in normal people (Joll, 1932). Joll remarks that it also occurs in all forms of goitre, in myotonia congenita, and in all cases of proptosis.

Present Investigation

In order to determine the approximate incidence of lid lag in people without thyroid disease, and to see whether it was particularly common in cases of peptic ulcer, 600 people of all ages and approximately equal sex numbers who attended a general hospital were examined. All patients with dysthyroidism, severe illness, and prolonged pyrexia were excluded. Otherwise there was no selection, except that 38 extra cases of peptic ulcer were specially included. Other manifestations which occur in thyrotoxicosis were also looked for in this series. Preference for hot or cold weather was noted, and the subjects were questioned about excessive sweating. Lid lag, lid retraction, exophthalmos, enlargement of the thyroid gland, and tremor of the outstretched fingers were looked for. The heights and weights of all those over 18 were noted where practicable.

For present purposes lid lag is defined as occurring when a white band of sclera appears between the upper lid and the cornea on following a moving object downwards with the eyes. If lid retraction is present lid lag can be considered to exist only if there is a definite widening of the band of sclera already visible. This is the most objective way of defining lid lag, although in those whose lid is usually held at a low level there may be a degree of lagging of the upper lid without any sclera coming into view. The results are shown in Table I.

TABLE I.—*Results of Investigation*

	Total No.	No. with Lid Lag
Whole series	600	85† (14%—or 10% of whole series excluding ulcer cases)
Patients with peptic ulcer ..	76	23 (33%)
,, ,, lid retraction ..	14	8 (57%)
,, ,, exophthalmos	3	3 (100%)
,, ,, non-toxic goitre	35	5 (14%)
,, ,, fine tremor ..	11	

† 58 males, 27 females.

Types of Eyelid Movement.—All cases of lagging of the upper eyelid were not alike. The band of sclera might appear during the whole movement of the eyeball or during any part of it. In other words, the lag might begin as soon as the eyeball started to descend, or the lid might move normally at first and lag later. The movement might be smooth or jerky. The lag in some cases was variable, at times being pronounced and at other times not being elicited at all. In five cases it was unilateral, and in two there was actually a reverse or upward movement of the eyelids as the eyeballs started downward. In one person the lid retraction was unilateral.

Lid Lag in Relation to Other Observations

The male sex predominated in the ratio of 2 to 1. All age groups produced subjects with lid lag, but it was more common in those over 40 (see Table II).

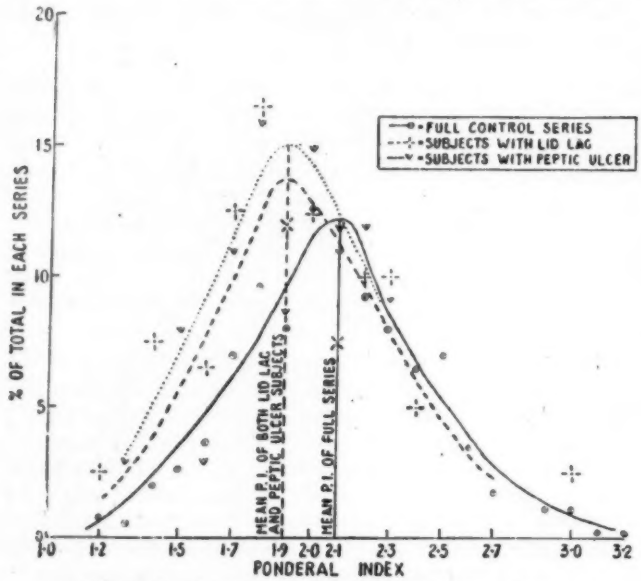
TABLE II.—*Age Incidence of Lid Lag*

Age	Total No. of Subjects	No. with Lid Lag
0–9 years	31	3 (9·7%)
10–19 ,, ...	50	2 (4%)
20–29 ,, ...	50	2 (4%)
30–39 ,, ...	72	8 (11%)
40–49 ,, ...	115	20 (17·4%)
50–59 ,, ...	132	22 (16·6%)
60–69 ,, ...	107	21 (19·6%)
70–79 ,, ...	43	7 (16%)

Eight of the 14 subjects with lid retraction also showed lid lag, as did all three with exophthalmos and five out of the 35 with simple goitres. Of the 76 cases of peptic ulcer 23 (33%) showed lid lag. This incidence is significantly higher than that of lid lag in the control series (10%). The impression was formed that lid lag was more common in thin people, and since peptic ulcer characteristically occurs in people with a low ponderal index (P.I.) (Draper, 1930; Robinson, 1938) this was suspected of being the explanation of the frequent occurrence of lid lag in peptic ulcer subjects. To test this hypothesis the P.I.‡ of all those over 18 was worked out, and all fell between 1.2 and 3.2. The number of subjects pertaining to each index was noted and expressed as a percentage of the whole. Thus three subjects (0.5% of the total) had a P.I. of 1.3. These percentages for each P.I. referring to (1) all the subjects, (2) the peptic ulcer subjects, and (3) those showing lid lag were plotted separately (see Chart). The mean P.I. in the full control series was 2.1 (slightly in excess of the mode), while in subjects with peptic ulcer and in those showing lid lag it was 1.9. The chart thus confirms the tendency for lid lag to occur in people of slim build, but it seems unlikely that this factor alone can explain its excessive appearance in peptic ulcer subjects. However, the male preponderance in both peptic ulcer—about 4 : 1 (Stewart, 1923; Ryle, 1932; Tidy, 1944;

*Based on a paper read at the South African Medical Congress, Capetown, September, 1949.

‡The ponderal index in this investigation was calculated by dividing the weight in pounds by the height in inches.



Graph showing percentage of each ponderal index.

Sallström, 1945)—and lid lag—2 : 1 in this series—may also offer a partial explanation.

Other Findings.—The occurrence of 28 cases of greatly enlarged non-toxic thyroid glands in subjects resident in Birmingham puts the approximate rate of simple goitre in this city at 5.6%. It was noted that 125 people preferred cold weather, 273 hot weather, and the remainder were indifferent. All subjects under 20 preferred the heat. Therefore only in young people can preference for cold weather be considered an important diagnostic feature in borderline hyperthyroidism, unless there has been a recent change in preference.

Assertions of excessive sweating were not uncommon, but revealed nothing of particular interest. The very fine rapid tremor generally considered characteristic of hyperthyroidism was found 11 times.

Mechanism of Lid Lag

Von Graefe (1864) believed that the cause of his sign was a disturbance of lid musculature, probably affecting Müller's muscle through the sympathetic system. He observed that morphine abolished the sign. Pochin (1939) believed that the lid retraction (usually combined with lid lag) in Graves's disease was associated with spasm of the levator palpebrae superioris and not with affection of the involuntary muscle. Joll (1932) considered that lid lag was often a "mechanical consequence of forward displacement," but this cannot explain its occurrence in normal people. The observations reported above do little to elucidate the mechanism of the lagging, but suggest that it is more common in thin people.

Summary

The examination of 600 subjects demonstrated the frequency of lid lag, apart from its hyperthyroid connexions. The incidence of certain other signs characteristically occurring in thyrotoxicosis was also estimated in this series. It seems that lid lag is particularly common in people suffering from peptic ulcer, and so cannot be of help in the diagnosis of mild degrees of hyperthyroidism in patients with ulcer.

Statistical Note

(1) The male sex preponderance is very highly significant, the difference between proportions being ten times the standard error.

(2) The high incidence of lid lag in peptic ulcer subjects is also significant. The differences between percentages is three times the standard error.

(3) The difference between the mean P.I. of ulcer cases and of the control series and between lid lag cases and controls is over three times the standard error in each instance. The apparent high frequency of lid lag in thin people and in ulcer subjects is thus highly significant.

I should like to thank Mr. Kelman, the medical superintendent, for permission to investigate patients at Selly Oak Hospital.

References

Draper, G. (1930). *Disease and the Man.* Macmillan, New York.
Eason, J. (1927). *Exophthalmic Goitre.* Oliver and Boyd, Edinburgh.
Jackson, W. P. U., and Pinkerton, G. E. (1949). In the press.
Joll, C. A. (1932). *Diseases of the Thyroid Gland.* Heinemann, London.
Pochin, E. E. (1939). *Clin. Sci.*, **4**, 91.
Robinson, S. C. (1938). *Illinois med. J.*, **73**, 210.
Ryle, J. A. (1932). *Lancet*, **1**, 327.
Sällström, T. (1945). *Acta med. scand.*, **120**, 288.
Stewart, M. J. (1923). *British Medical Journal*, **2**, 955.
Tidy, H. L. (1944). Ibid., **1**, 677.
von Graefe, A. (1864). *Dtsch. Klinik*, **16**, 158.

ACTINOMYCOTIC EMPYEMA

BY

HAROLD W. BOWYER, M.D.

Assistant Visiting Physician, Bolton Royal Infirmary

Massive empyema due to actinomycosis is uncommon enough to warrant description of a case. Price (1941) states that the empyema is rarely large and the primary lesion seldom pleural. Until recently the prognosis was regarded as unfavourable, death resulting from exhaustion and toxaemia. Penicillin therapy, however, has given promising results in cases cited by Hamilton and Kirkpatrick (1945) and others in this country, and by American authors.

The following case is of interest because a total dosage of over 25,000,000 units of penicillin extending over a period of 56 days was necessary to overcome the infection. Repeated aspirations were necessary owing to the encysted nature of the empyema.

Case History

A carter aged 49 was seen by me in consultation with his own doctor on February 12, 1949. He gave a history of sudden onset of right-sided chest pain and rigors on December 22, 1948. After a few days in bed he resumed his normal activities but did not feel well. On January 29, 1949, the pain returned accompanied by cough and feverishness. His doctor suspected a pleural effusion, but was unable to obtain fluid from the pleural cavity. The temperature was remittent and the dullness increased in spite of treatment with sulphamezathine. The patient had frequent profuse sweats, looked toxic, and had lost weight.

I found him to be moderately dyspnoeic. His pulse rate was 84, regular, and of good volume; respirations, 28; temperature, 101.3° F. (38.5° C.). The apex beat was in the fifth interspace outside the nipple line. His blood pressure was 140/75 mm. Some clubbing of the fingers was present. Examination of the chest showed well-marked signs of a pleural effusion, with stony dullness extending from the base of the right lung to the third interspace posteriorly and forward to the anterior axillary line. B.S., V.F., and V.R. were greatly diminished. There was no bulging of the intercostal spaces. An area of paravertebral dullness was found on the opposite lung. The urine showed no abnormality.

On February 13 he was admitted to the Bolton Royal Infirmary. A radiograph revealed a massive pleural effusion of the right side of the chest, and 10 ml. of thin greenish foul-smelling pus was aspirated and sent to the pathology department. The patient was then put on penicillin, 250,000 units daily in three-hourly injections. On February 24, on receipt

of the pathological report, the dosage was increased to 500,000 units daily.

Pathological Report.—Greenish foul-smelling pus containing a moderate number of small yellow granules. Stained film: numerous pus cells, numerous fusiform bacilli, small Gram-negative coli and bacilli, a moderate number of clumps of filamentous organisms of fungal morphology. This specimen was referred to the Fungus Reference Laboratory, which reported that *Actinomyces israeli* was present.

On February 22, 2 pints (1.14 litres) of pus was aspirated and 100,000 units of penicillin injected. On February 24, 1 pint (570 ml.) was aspirated. A radiograph on February 28 still showed an encysted collection in the right mid-zone posteriorly. This was much thicker and more difficult to aspirate. Rib-resection was considered, but as the fluid was centred under the inferior angle of the scapula it was decided to continue to aspirate.

By March 12 the temperature finally settled. On the 14th a radiograph still showed some encysted fluid. Aspiration failed. On March 18, 6 oz. (170 ml.) of pus was aspirated after screening, and penicillin was injected. On April 8, 6 oz. of pus was aspirated and 100,000 units of penicillin injected.

Pathological Report of Pus.—On March 9:—Direct smear: numerous pus cells, very scanty Gram-negative bacilli, no actinomyces seen. Cultures: no growth on blood agar. On March 18:—Direct smear: numerous pus cells, no organisms. Culture (aerobic and anaerobic): no growth.

An *x*-ray report on April 12 stated that the fluid seemed to have cleared from the right side and had left some residual pleural thickening.

Other Investigations.—A blood count on February 14 showed: Hb, 68%; red cells, 4,435,000; colour index, 0.77; white cells, 14,000 (eosinophils 81.5%, basophils 0.5%, lymphocytes 11.5%, monocytes 6.5%). Sputum examination on February 17: *M. tuberculosis* not found; moderate number of pus cells, fairly numerous epithelial cells, a few "dust" cells; no malignant cells seen. Blood sedimentation rate on February 21: first hour, 118 mm.; second hour, 125 mm. (Westergren). Sputum on February 25: moderate number of pus cells, fairly numerous squamous cells, fairly numerous dust cells, no malignant cells; *M. tuberculosis* not found. Culture:—Mixed: haemolytic streptococci and *Neisseria catarrhalis*.

In addition to intramuscular penicillin (total dosage 25,000,000 units) and intrapleural penicillin (400,000 units) the patient received potassium iodide, 30 gr. (2 g.) thrice daily.

He was discharged home on April 18, having been ambulant for ten days. He had gained weight and looked and felt very well.

I am greatly indebted to Dr. G. Manning, pathologist; Dr. Brash, radiologist; and Dr. Dawson, resident medical officer, for their assistance in the investigation and treatment of this case.

References

Hamilton, A. J. C., and Kirkpatrick, H. J. R. (1945). *British Medical Journal*, **2**, 728.

Price, F. W. (1941). *Textbook of Practice of Medicine*, 6th ed., p. 1,269. Oxford Medical Publications.

The American Heart Association is publishing a quarterly journal entitled *The American Heart*, the object being to obtain broader public understanding and support of the association's programme in the field of cardiovascular disease. Approximately $700,000 has been allocated for heart research this year by the association and affiliated organizations. According to a report in the *New York Times* (September 13, 1949) the United States Public Health Service is also launching a nation-wide attack on heart disease. A programme involving expenditure amounting to over $8,000,000 has been planned by the National Heart Institute. Among the subjects which are to be specially studied are: environmental and hereditary factors; dietary factors; new surgical methods; the usefulness of new drugs and new substances such as ACTH and cortisone; new diagnostic instruments such as the electrokymograph and the ballisto-cardiograph.

Medical Memoranda

Unusual Case of Nutritional Anaemia

The following case of nutritional anaemia is worthy of record because of the history.

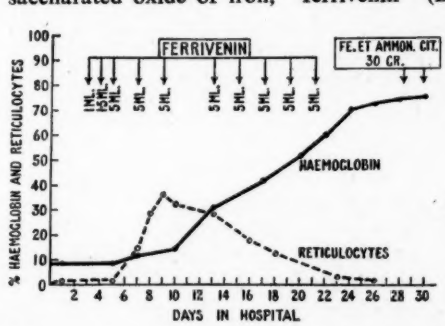
Case Report

A boy aged 9 was admitted to hospital on May 25, 1948, with a history of recurrent vomiting for six weeks. His previous medical history showed that he had been a full-time baby, born spontaneously after a normal pregnancy. He was the sixth of a family of seven, and all his siblings were healthy. From birth there had been a spastic paralysis of all his limbs; he had never been able to sit up and was completely helpless. Since birth his diet had consisted of milk. He refused to eat any other foods and would take his milk only from a feeding-bottle. His average daily consumption was about 5 pints (2.84 litres).

He had always tended to be constipated, but otherwise remained well until ten weeks before admission to hospital, when he had become unusually constipated and had had no bowel action for 25 days, at the end of which time he passed a very large constipated stool. Since then he had been less keen on sucking; he had often vomited after feeds, and his condition had steadily deteriorated.

On examination he was seen to be grossly mentally deficient, and was unable to speak. The skull was flattened posteriorly and there was a scoliosis of the dorsal spine. His temperature varied from 100 to 101° F. (37.8 to 38.3° C.); he was extremely pale and his face was puffy. His teeth were larger than normal, well spaced, and not carious. There was a spastic paralysis of all limbs, with permanent flexion of the elbow- and knee-joints due to contractures. Cardiac enlargement was not pronounced, but a loud blowing systolic murmur was heard all over the praecordium. A blood count showed: Hb, 8.5%; red cells, 1,020,000; C.I., 0.42; white cells, 11,400 (polymorphs 54%, basophils 1%, lymphocytes 38%, monocytes 7%). The red cells were severely microcytic and hypochromic. These figures were confirmed by the Department of Medicine, Aberdeen University. Plasma proteins were 7.7 g. %, with an albumin/globulin ratio of 1.24 to 1. A radiograph showed abnormally slender bones with delayed ossification and severe general decalcification.

The patient refused to take iron by mouth, and in view of this and the extreme degree of anaemia it was decided to give iron by intravenous injection. The preparation used was a saccharated oxide of iron, "ferrivenin" (Bengers), which contained 20 mg. of iron per ml. Small doses of 1 ml. and then 1.5 ml. were given on consecutive days at the beginning of treatment, and thereafter 5 ml. on alternate days to a total of 42.5 ml. On the day after the third injection the temperature rose to 104° F. (40° C.), but, despite this, the patient looked much better. One injection was omitted, and his temperature settled. He remained afebrile during the remainder of the treatment.



The haemoglobin and reticulocyte response to therapy are shown on the accompanying Chart. Within three weeks the haemoglobin was 70%, and he had been persuaded to increase the range of fluid feeds, but he still refused all solids. Iron and ammonium citrate in 10-gr. (0.65-g.) doses was thereafter given three times daily in bottle feeds.

COMMENT

The only demonstrable dietary deficiencies in a boy of 9 fed since birth solely on milk were a severe iron-deficiency anaemia and poor calcification of bones. Milk as a food is an incomplete source of nourishment, but in such large quantities as this patient consumed there is an adequate supply of all the essential food elements except iron. The vitamin D supply is variable, but is probably insufficient in the absence of sunlight. The response to intravenous iron was rapid, and the injections were well tolerated.

M. MCLEAN, M.B., Ch.B., D.C.H.,
Medical Registrar,
Royal Aberdeen Hospital for Sick Children.

An Extrarenal Hypernephroma

The following case was shown at a pathological meeting of the Section of Surgery of the Royal Society of Medicine on January 7, 1948.

CASE REPORT

The patient, a man aged 58, was first seen at Edgware General Hospital in October, 1944. He had had sacro-iliac backache for two years, but nothing significant was found on examination. He also complained of dysuria and nocturnal frequency in December, 1945, when the backache and urinary symptoms had increased, and of lassitude and loss of weight.

On examination his general appearance was cachectic. A large solid tumour was found emerging below the left costal margin and filling the upper left quadrant of the abdomen and the epigastrium. It moved on respiration, was dull to percussion, and was not tender. The liver was not enlarged and there was no ascites. The blood pressure was 120/70. A blood count showed: red cells, 4,000,000; haemoglobin, 78%; white cells, 10,800. The urine was normal. Radiographs of the spine revealed osteoarthritis but no metastatic deposits. Barium studies showed the stomach displaced to the right and hypertrophy of rugae at the greater curvature; the splenic flexure was displaced downwards. An intravenous pyelogram showed the left kidney rotated and displaced downwards to the level of L4. Anatomy and function were normal.

Operation (January, 1947).—A left paramedian incision was made. A normal spleen presented in the epigastrium on the surface of a large retroperitoneal tumour. The spleen and tumour were excised after freeing the latter from the upper pole of the kidney. A tough layer of connective tissue containing the suprarenal gland intervened. Recovery was uneventful.

The specimen is a solid ovoid tumour weighing 7½ lb. (3.4 kg.) (Fig. 1). Microscopically, the appearances are characteristic of a hypernephroma. The cells are polygonal, with a foamy cytoplasm. The connective-tissue septa are thinner and less abundant than usual (Fig. 2).

COMMENT

Tumours with the histological appearance of adrenal carcinomata—the so-called hypernephromata—occur much less commonly as independent retroperitoneal growths than within the substance of the kidney.

Surveys of large numbers of primary retroperitoneal tumours (Goebell, 1901; Donnelly, 1946) indicate that adrenal-cell tumours account for only 3 or 4%; the remainder consist of a wide range of tumours corresponding to all the varieties which may occur in the adult urogenital organs. They are thought to arise from remnants of the embryonal urogenital apparatus (Hansmann and Budd, 1931). Death results from dissemination by lymphatics and veins as well as from direct extension to vital organs. Bone metastases are relatively infrequent (Ewing, 1940).

Complete extirpation of the tumour while still self-contained obviously offers the best prospects of cure. The operability rate is generally low because symptoms are ill defined and may remain so for months or years before a mass is discovered. Of Donnelly's (1946) series of 95

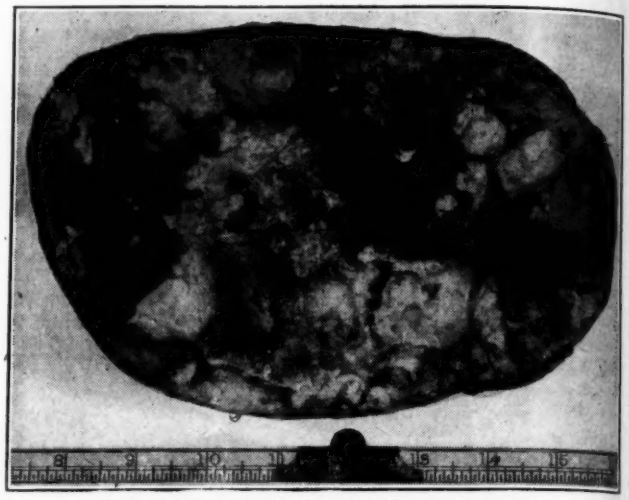


FIG. 1.—Photograph of cut surface of tumour.

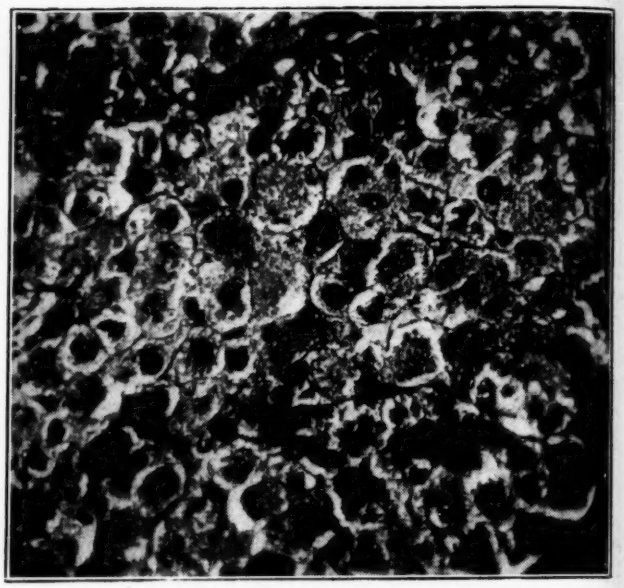


FIG. 2.—Photomicrograph of tumour—high power.

primary retroperitoneal tumours, 82 were explored and 34 were considered operable. The operative mortality was 19.7%.

The most valuable diagnostic aids to earlier diagnosis are barium *x*-ray films and pyelography, which reveal displacements of the viscera and exclude growths of the gastro-intestinal and urinary tracts. Loss of weight and strength are the most constant symptoms. Exploratory laparotomy, however, often offers the only means of discovering the exact nature of the tumour.

I am indebted to Miss M. H. Shaw for the photographs.

FRANK FORTY, F.R.C.S.

REFERENCES

Donnelly, B. A. (1946). *Surg. Gynec. Obstet.*, **83**, 705.
Ewing, J. (1940). *Neoplastic Diseases*, 4th ed., p. 824. Philadelphia.
Goebell, R. (1901). *Dtsch. Z. Chir.*, **61**, 1.
Hansmann, G. H., and Budd, J. W. (1931). *Amer. J. Path.*, **7**, 631.

Reviews

NEUROHISTOLOGY

Atlas of Peripheral Nerve Injuries. By William R. Lyons, Ph.D., and Barnes Woodhall, M.D. (Pp. 339. £4.) Philadelphia and London: W. B. Saunders Company. 1949.

This superbly produced monograph is concerned chiefly with the histological appearances of damaged nerves removed at operation. It is not a complete atlas of peripheral nerve injuries as there are few clinical photographs, and none illustrating motor or sensory disturbances. But provided that these limitations are recognized the reader will not be disappointed.

The American organizations for treating war injuries of the peripheral nerves were a good deal less compact than our own. There was no one comparable with George Riddoch to guide policy, and in consequence some of the work was done by men of relatively limited experience and without any predetermined plan. Although this diversity had obvious drawbacks there were some compensations, one of which was the immense variety in the material sent for histological examination. Variations in time between injury and operation were most significant, some nerves being repaired earlier, and others much later, than was the practice in the British nerve injury centres. Some surgeons amused themselves by wrapping the suture line with various materials and later gave the pathologist the chance of observing the effect of these wrappings on the underlying nerve. The result is an atlas of the morbid anatomy of nerve injuries in man which is as complete as surgical considerations will permit. Indeed, the profusion of beautiful photomicrographs is such that the reader begins to feel the aching behind the eyes and the painful swelling of the ankles that afflict the earnest picture-gazer who has spent a whole day at the Louvre. Some of the photographs are frankly repetitious, and their omission would have been beneficial.

Modern neurohistology is so enchanting that the morbid anatomist will enjoy this collection simply as an exhibition of the astonishing diversity of morphological changes that result from nerve injury and regeneration. This work is not only a great credit to its authors: it is a tribute to all who have contributed to the perfection of staining methods for nervous tissue and to modern photomicrography. The surgeon's interest will be different. He will realize the extent to which his practice must be guided by the findings of the morbid anatomist. The tissue disturbance caused by a fast-moving particle is far more widespread than usually supposed, and in no tissue are its effects more clearly revealed than in the peripheral nerve. In consequence, the stumps of a nerve severed in a war wound must be resected more generously than those of a nerve damaged in an industrial or domestic accident. He will find that the theoretically ideal primary suture is unsatisfactory in practice. He will learn something about the curious pathology of traction injuries which (it is hoped) will convince him that operative intervention is not likely to be of much use. He will learn, too, about the fate of autogenous and homogenous grafts.

This is not a book for bedtime reading; it is not one that should be in every surgeon's and morbid anatomist's library; but it is a work that should be in the possession of everyone who has any interest at all in the peripheral nervous system. The authors hope that, "if the professional, administrative, and financial hazards of surveying large groups of rehabilitated war veterans can be surmounted through governmental or private channels, the influence upon peripheral nerve regeneration of the neuropathological changes that have been described in this atlas will be the subject of a separate monograph within the next few years." Perhaps it may encourage them to know in advance how much further we shall be in their debt if they succeed, as we trust they will, in this second and more formidable undertaking.

H. J. Seddon.

PULMONARY NEOPLASMS

Bronchiogenic Carcinoma and Adenoma. By B. M. Fried, M.D. (Pp. 306; 118 illustrations. £1 13s.) London: Baillière, Tindall and Cox. 1948.

This book, which discusses a subject that has achieved in recent years a practical importance that it will maintain, is a useful study but not an authoritative account. The illustrative radiographs are below the standard one expects to-day, and not one lateral picture is used. Some of the radiographs are produced as negatives and some as positives—uniformity is preferable. The photographs of specimens are very poor.

It is disturbing to see the term "superior pulmonary sulcus tumour" perpetuated, for the name means little or nothing and should be abandoned. In the description of metastases it is stated that the liver is involved in about 40% of cases, and the contralateral lung in about 30%. Although not specifically stated, one presumes that these are necropsy figures, for they are certainly not true of present clinical practice in England. The policy of using observations made in the necropsy room projected backwards to embellish a clinical picture is liable to be most unsatisfactory and, although having its uses, is somewhat out of date. Far too much teaching in the past has been of advanced disease, which renders it more difficult for the student and practitioner to recognize the earlier phases when they meet them before the stage of impending death.

A great deal of the space devoted to case histories might have been better used in a fuller discussion of such a dangerous topic as aspiration biopsy, or a more detailed consideration of the significance of pleural fluid, or of bronchoscopy, or of a number of other fundamental matters. The remarks on radiotherapy and surgery are purely "scissors and paste" products and carry no direct authority. Bronchial carcinoma is to-day a surgical disease, and the surgery section should either be written by a surgeon or omitted. The chapters on bronchial adenoma are indifferent, and it is difficult to see why the one on mediastinal tumours was included at all.

The book contains a full bibliography and is of value as a work of reference for this, and for the reviews of the incidence and aetiology of the condition.

R. C. Brock.

OPERATIVE SURGERY

Operative Technic in General Surgery. Edited by Warren H. Cole, M.D., F.A.C.S. With introduction by Frank H. Lahey, M.D., F.A.C.S. (Pp. 951; 521 figures. No price.) New York: Appleton-Century-Crofts, Inc.

The latter part of the nineteenth century might be described as the Elizabethan period of operative surgery, when enterprise was so widespread and the field so fruitful that achievement was great. This rich era of technical advance was consequent upon the discovery of the causes of infection and their mastery. Since then some surgeons have thought the harvest had been fully reaped, and from time to time even great leaders like Erichsen and Moynihan made the mistake of expressing such an opinion. Great

advances have nevertheless been made in recent years, and no doubt there are others to come.

An account of some of the recent advances will be found in this book, which is edited by Professor Warren H. Cole, of Chicago, who was recently in this country and visited all the university clinics. The work is compiled by 34 well-known American surgeons. There are sections on abdominal incisions, by Frederick A. Coller and K. F. Maclean; on the surgery of the stomach and duodenum, by Waltman Walters and L. R. Dragstedt; on the thyroid, by J. de J. Pemberton and B. M. Black; on vascular lesions, by Daniel Elkin and M. E. DeBakey; on the hand by H. S. Allen and Sumner L. Koch; and on the pancreas and adrenal, by Alexander Brunschwig, to mention only a few of the distinguished contributors.

References (almost exclusively from American sources) follow certain sections, but in others they are scanty or absent. The printing is clear and the text easily readable; illustrations are plentiful, and the line drawings are good, though less is to be said for the few coloured plates. As a textbook of operative surgery it is open to the criticism of unevenness, since some of its aspects are discussed thoroughly and others scantily or not at all. Overlooking this, however, there will be found a series of articles by well-known masters for whom no commendation is necessary, and these alone will make the book attractive to many surgeons. Dr. Frank Lahey writes an introduction in which he points out that the book has the great advantage of being written by men experienced in the particular subjects about which they write. This is its great merit and compensates for any incompleteness of the subject-matter.

LAMBERT ROGERS.

THE THYROID

The Thyroid and its Diseases. By J. H. Means. Second edition. From the Thyroid Clinic of Massachusetts General Hospital. (Pp. 571. £3 12s.) Philadelphia and London: J. B. Lippincott Company. 1949.

Since the first edition of this book appeared in 1937 so many advances have been made that nearly all the sections have now been rewritten. Professor Means has been in close contact with most of these advances, so that he can present full, clear, and authoritative discussions of such subjects as the metabolism of iodine, the pharmacology and physiology of the thyroid and thyrotropic hormones, the pharmacology of the antithyroid drugs, the new light thrown on thyroid physiology by the use of radioactive iodine as tracer, and the use of this substance in therapy. All these and many more advances are lucidly explained and fairly discussed. Full and up-to-date accounts of the diseases of the thyroid are an important feature of the book. A valuable chapter is contributed by Oliver Cope on the surgery of the gland, with particular reference to the special knowledge required by the thyroid surgeon and the factors influencing his plan of operation. Professor Means's view on the place of antithyroid drugs is summarized by his conclusion that "drug therapy is certainly preferable to mediocre surgery," a statement which would be accepted in this country.

The diagnosis of hyper- or hypothyroidism is not always easy on clinical grounds alone. The author assesses the value and the shortcomings of the basal metabolic rate as a diagnostic aid, and discusses other tests of thyroid function. He points out, however, that laboratory tests do not in any way replace the clinical examination. The cold hand, dry or moist, almost excludes hyperfunction of the thyroid; an increasing need for bed covering is suggestive of myxoedema. The characteristic entrance of a thyrotoxic patient into the consulting-room is vividly described, equally the good nature of the myxoedematous person who often becomes still more pleasant when "thawed out by thyroid."

There is in this book much valuable information and instruction for all interested in the thyroid, and full lists of references at the end of each chapter provide the link with the original literature.

C. L. COPE.

COMMON-SENSE PSYCHIATRY

The Commonsense Psychiatry of Dr. Adolf Meyer. Edited by Alfred Lief. (Pp. 677. $6.50 or £1 19s.) New York and London: McGraw-Hill Book Company, Inc.

Most of the papers in this volume date from 30 or 40 years ago, and it is remarkable how fresh and topical they are to-day. This book contains not only a representative collection of Meyer's papers but a biography of their author and a history of psychiatry during the last 50 years. It shows how the author has led psychiatry away from an exclusive interest in cerebral lesions and toxins towards the actions, reactions, and attitudes of the individual towards the whole of his environment. Some such reactions are physical, some psychical, and some psychosomatic.

Meyer therefore takes a holistic attitude towards his subject and persistently refuses to be bound by dogmata of any sort. He accepts the modern dynamic psychology, and he studies the past as well as the present and does not insist on the universal influences of complexes, especially those founded on infantile sexuality. The mentally sick person is not the sum of elements of disease but a functioning unit in society who is doing something. Hence his insistence on the paramount importance of psychiatric social work and occupational therapy. Moreover, each patient is a problem in himself, and though classification may be useful for didactic purposes patients cannot be forced into nosological pigeon-holes. Meyer insisted that sanity depends on the endurance against strains—physical, psychological, and social—and such conditions as schizophrenia are disorganizations of both organic and functional habits. He stresses the importance of the school period in preventing such disorganization of habits by giving opportunity and encouragement to constructive and active behaviour. He has been a supporter of mental hygiene, child guidance, and all methods of preventive mental medicine.

Meyer's appointment to the directorship of the Phipps Institution at Baltimore gave him the opportunity to put all these constructive ideas into practice, his patients being principally early, recoverable cases. Towards the end of his long life he devoted thought to the more general aspects of psychiatry—those relating to such problems as freedom, marriage, education, and religion. Readers of this book will find not only a fascinating historical document but stimulating and informative material which will be most useful to them in their own work.

R. G. GORDON.

SPANISH HAEMATOLOGY

Symposium de Hematologia y Hemoterapia—1948. By J. Guasch, A. Raichs, C. Trincao, and R. Surinyach. (Pp. 522. No price.) Barcelona: Miguel Servet. 1949.

Mononucleosis Infecciosa. By J. J. Permanyer Macia and P. Vintró Marcé. Preface by Professor M. Soriano. (Pp. 96. No price.) Barcelona: Ediciones Byp. 1948.

Of the seven articles in the symposium of haematology and blood transfusion four are moderately interesting. Well-documented essays based on two cases each of elliptocytosis and pregnancy occurring in the course of chronic myeloid leukaemia present a clear account of the state of our knowledge of these rarities. A single case gives opportunity for

a discussion on the curative effect of splenectomy in antimony-resistant kala-azar—a subject which, though of little interest to us, is of considerable importance in paediatric practice around the Mediterranean Sea. Of the residents in the Barcelona area only 10% appear to be Rhesus-negative, in contrast to the 35% reported in Basques by Etcheverry and by Mourant. Short essays on allergy and intramedullary transfusion and an article of 228 pages on the treatment of severe neutropenia complete the volume. There seems to be little difference between standard practice in this country and that advised by the authors. This is the second volume of this type received from the Iberian peninsula within the last few months; both show great industry but little profit.

Macia and Marcé's short monograph gives a clear account of infectious mononucleosis and of the laboratory aids to its diagnosis. The clinical section follows Tidy in recognizing three main types of the disease—glandular, anginose, and febrile—but attention is drawn also to the bizarre symptom-complexes which sometimes occur. In the section on laboratory diagnosis the various modifications of the Paul–Bunnell reaction are lucidly described and evaluated. The clarity of the presentation throws the few omissions into relief. Three types of glandular fever cell described by Downey and McKinlay should have been mentioned, and the occurrence of 1–7% of the Type I cells of these workers in infective hepatitis and other virus diseases is sometimes significant. The great increase in staff-form neutrophils over segmented types in the early stages of the disease is of considerable diagnostic value, and the recognition of epidemic outbreaks in which the Paul–Bunnell reaction is consistently negative (recorded in this country by Macfarlane) is very important. The bibliography, though it includes most of the important papers, could well be enlarged. The volume is completed by some long abstracts from the foreign press. It is an unpretentious, useful monograph for isolated workers who read Spanish.

GEORGE DISCOMBE.

Dentistry in Public Health, edited by Walter J. Pelton and Jacob M. Wisan (pp. 363; £1 7s. 6d.; Philadelphia and London: W. B. Saunders Company; 1949), is an interesting book by many contributors which illustrates the interest now taken in dentistry from the public health viewpoint in the United States. A considerable amount of research in the last few years has produced valuable results, including the discovery of the role of fluorine in the prevention of caries. It is unfortunate that publicity has been given at times to work and theories that have not been fully evaluated, but in this book evidence is sifted and conclusions are not accepted without adequate supporting facts. Thus, in spite of much that has been written on the subject, it is stated that the topical application of fluorides to the teeth as a preventive measure has not yet been substantiated. It is of interest to see the extensive programme for research into public health dentistry that is proposed. It would be as well if we gave more thought to the subject in this country.

The monograph by the late Dr. Libman and Dr. Friedberg, *Subacute Bacterial Endocarditis* (edited by Henry A. Christian and reprinted from Oxford Loose-Leaf Medicine; pp. 113; illustrated; £1 1s.; New York and London: Geoffrey Cumberlege, 1949), is a comprehensive and valuable work based upon large numbers of cases. The pathology, diagnosis, and treatment are presented in detail, but the authors have focused little attention on this infection in congenital heart disease. It is in such patients, in whom the myocardium remains unscathed, that the best results of therapy with antibiotics are to be expected. There is no reference to an important diagnostic method in non-cyanotic congenital heart disease—the use of an arterial as opposed to a venous blood culture when there is a left-to-right shunt. Any means of determining the diagnosis more quickly is of added value now that specific remedies are available. Of interest to readers in this country will be the good colour plate showing Janeway lesions, but the other illustrations are indifferent. A comprehensive bibliography completes and enhances the value of this authoritative monograph.

BOOKS RECEIVED

[*Review is not precluded by notice here of books recently received*]

The Healing Touch. By H. Williams. (Pp. 406. 15s.) London: Jonathan Cape. 1949.

Freedom from Want. Edited by E. E. DeTurk. Foreword by N. E. Dodd. (Pp. 207–84. $2.00.) Waltham, Mass.: The Chronica Botanica Co. London: Dawson. 1949.

Psycho-Analysis—a Modern Delusion. By F. Kenyon. (Pp. 141. 5s.) London: The Pioneer Press. 1949.

Population Trends and the World's Biological Resources. By G. C. L. Bertram, M.A., Ph.D. No. 5. (Pp. 38. 2s.) London: The Eugenics Society, and Cassell. 1949.

The Medical Clinics of North America. Mayo Clinic Number. Gastro-Intestinal Conditions. (Pp. 923—1,210. No price.) London and Philadelphia: W. B. Saunders. 1949.

Pedigrees of Negro Families. By R. Ruggles Gates, F.R.S. (Pp. 267. $5.50.) Philadelphia and Toronto: The Blakiston Company. 1949.

Lehrbuch der Inneren Medizin. By H. Assmann, G. v. Bergmann, and others. Foreword by H. Schwiegk and A. Jores. Vols. 1 and 2. Berlin: Springer. 1949.

Children of Today and Tomorrow. By E. Dukes and M. Hay. Preface by D. Mace, Ph.D. (Pp. 249. 12s. 6d.) London: George Allen and Unwin. 1949.

Office Management for Health Workers. By F. King and L. L. Feldman. (Pp. 164. 12s. 6d.) New York: The Commonwealth Fund. London: Geoffrey Cumberlege. 1949.

Kinderärztliche Notfallfibel ein Exkurs fur die Praxis. By B. de Rudder. (Pp. 134. M. 7.80.) Stuttgart: Georg Thieme. 1949.

Aus dem Leben Fritz Richard Schaudinns. By C. Kuhn. (Pp. 73. M. 3.80.) Stuttgart: Georg Thieme. 1949.

Transactions of the Ophthalmological Society of the United Kingdom. Vol. 67. (Pp. 530. 40s.) London: Churchill. 1948.

Medullary Nailing of Küntscher. By L. Böhler, M.D. Translated by H. Tretter, M.D. (Pp. 386. 38s. 6d.) London: Baillière, Tindall and Cox. 1948.

Communicable Diseases and their Nursing Care. By E. Pearce, S.R.N. Foreword by W. Gunn, F.R.C.P. (Pp. 392. 14s. 6d.) London: Faber. 1949.

The Human Body and its Functions. By C. H. Best, C.B.E., M.D., F.R.S., and N. B. Taylor, V.D., M.D., F.R.S.Canad. 2nd ed. (Pp. 500. 18s.) London: Chapman and Hall. 1949.

A New Dictionary of Chemistry. Edited by S. Miall, LL.D., B.Sc., and L. M. Miall, B.A., F.R.I.C. 2nd ed. (Pp. 589. 60s.) London: Longmans, Green. 1949.

Modern Practice in Ophthalmology, 1949. Edited by H. B. Stallard, M.B.E., F.R.C.S. (Pp. 525. 65s., plus 1s. 6d. postage.) London: Butterworth. 1949.

Lippincott's Quick Reference Book for Medicine and Surgery. By G. E. Rehberger, A.B., M.D. 14th ed. (Pp. 1,723. £6.) Philadelphia, London, and Montreal: Lippincott. 1949.

A Study of Certain British Seaweeds and their Utilisation in the Preparation of Agar. By S. M. Marshall, L. Newton, and others. Edited by L. Newton. (Pp. 184. 27s. 6d.) London: H.M.S.O. 1949.

The New York Academy of Medicine. Its First Hundred Years. By P. Van Ingen. (Pp. 573. 55s.) New York: Columbia University Press. London: Geoffrey Cumberlege. 1949.

Principles of Human Physiology (Starling). By C. Lovatt Evans, F.R.C.P., F.R.S. Chapters on Special Senses by H. Hartridge, M.D., F.R.S. 10th ed. (Pp. 1,193. 42s.) London: Churchill. 1949.

BRITISH MEDICAL JOURNAL

LONDON

SATURDAY OCTOBER 15 1949

WORLD MEDICAL ASSOCIATION

Medical men and women from 27 countries met this week at B.M.A. House to take part in the deliberations of the General Assembly of the World Medical Association. The groundwork of the meeting had been prepared the week before by the ten members of the WMA Council under the chairmanship of Dr. T. C. Routley, Secretary of the Canadian Medical Association. Dr. Charles Hill, Secretary of the B.M.A., is the new President of the WMA for 1949–50 in succession to Professor Eugene Marquis. The machine of the WMA is kept moving on its appointed course by the Secretary-General, Dr. Louis H. Bauer, of New York, who is also Chairman of the Board of Trustees of the American Medical Association. He is helped by Assistant Secretaries for Asia, Australasia, Europe, and Latin America in the persons of Dr. S. C. Sen, Dr. J. G. Hunter, Dr. Paul Cibrie, and Dr. J. A. Bustamante. The financial affairs of WMA are kept in order by the treasurer, Dr. O. Leuch, of Zurich.

The WMA has progressed far and fast since the first meeting of the General Assembly in Paris in 1947. It is now a well-organized and hard-working affair; its objects, constitution, and rules are laid down in black and white; and through the work of its committees and Council it is now well on the way to achieving the objects it has set itself. It has established relations with the World Health Organization and with Unesco, and no doubt in time it will define in co-operation with these governmental organizations those fields of activity which lie within the province of the WMA. Three issues of the WMA *Bulletin* have now appeared under the editorship of Dr. Morris Fishbein, who is also editor of the *Journal of the American Medical Association*. The *Bulletin* places on permanent record in English, French, and Spanish the results of the WMA's work, and contains matter that should be of great interest to all practising doctors who now all over the world are witnessing increasing governmental control of their professional lives. The WMA, it is important to note, is a voluntary association of the various national organizations, such as the A.M.A. and the B.M.A., which represent and protect the interests of medical men and women in various countries of the world. WHO and Unesco, being specialized agencies of the United Nations, are officered by men and women chosen by the governments represented in the United Nations. Between these official governmental agencies and the unofficial voluntary WMA there should be ample room for co-operation.

This week the Assembly once more had before it the text of the International Code of Ethics—what might be called a revised version of the Hippocratic Oath. The need for this was felt because of the crimes committed by German medical men during the recent war, a report on which was one of the early activities of the WMA. It is of course not easy to draft a code that will conform with the ethical standards of various countries, these being so intimately linked with the various world religions. So it has been proposed that each nation must be able to vary the code, so long as its main principles are not infringed. Ten national associations have already adopted it as it stands.

Last week the Council gave much time to a study of a long report on postgraduate education, and finally agreed that "after the training ordinarily prescribed in a medical school course there should be an additional period of training in an approved post before engaging in independent practice." It was felt strongly that an effort should be made to increase the facilities for postgraduate study in countries foreign to the postgraduate, although it was realized that certain legal difficulties might be an obstacle, which the national medical associations are being asked to try to overcome. Another important proposal which came before the Assembly was for an investigation into the social security schemes existing in different countries and their effect upon the quality and efficiency of medical services and also upon the relationship between doctor and patient. Such a study would seem to be of the highest value in these days of rapid change. In relation to this an inquiry is to be made into the medical man-power in different countries, a subject in which there seems to be much interest. Among some of the other matters considered was the question of distributing medical journals and textbooks, in connexion with which Unesco has done useful work in promoting international co-operation between national libraries. Unesco, it may be recalled, is trying to co-ordinate the meetings of international medical congresses so that there will be no overlapping in the timetable of these, but from the words used in a Unesco document on this subject the WMA is asking Unesco whether it is to be understood that it is seeking to determine the agenda of these congresses. This would seem highly unlikely, but clarification is clearly needed.

The general work of this week's Assembly will be summarized in next week's *Journal* so that the reader may have an idea of how WMA is setting about achieving the first of its objects, which is "to promote

closer ties among the national medical organizations and among the doctors of the world by personal contact and all other means available." The second object is "to maintain the honour and protect the interests of the medical profession"; and the last, more difficult or even impossible to realize, is "to promote world peace." At least one step towards world peace is the voluntary meeting together of medical men and women from different parts of the world to discuss all those ways and means of furthering the aim of every doctor—the care of the sick, the prevention of disease, and the maintenance of health. In this work it is to be deplored that the medical profession of the U.S.S.R. and its satellite countries does not see fit to take part—eloquent testimony to the perils of the political control of medicine.

MR. BEVAN'S REVIEW OF N.H.S.

A large crowd of journalists gathered in the Ministry of Health last week to hear Mr. Aneurin Bevan give a review of the first year of the National Health Service. This he did in a skilful and disarming manner, and as advocate in his own cause obviously could not be expected to expose those deficiencies in the Service which the medical profession now sees. One year, he said, was a very short time on which to base a judgment, but he claimed that "the first year has been remarkably good," and for this paid his tribute to all those who were concerned in the transition. The Health Service must be seen as a gigantic change-over from the private pocket to the public purse, and when he was asked later how far actual expenditure had exceeded that originally estimated in the White Paper he replied, "I should think about twice." A Select Committee of the House of Commons has already investigated the expenditure in the N.H.S. and there are obviously many factors that must have made a more exact estimate difficult. But if the Minister can make one mistake of such magnitude it is not out of the question that he may make another. For example, to a question about the remuneration of general practitioners he answered: "So far there is conclusive evidence that we have more than honoured the Spens recommendation." One point that emerged clearly from the recent discussions between the B.M.A. and the Ministry of Health was that the evidence was by no means conclusive. Then again, when he was asked whether he did not think that the remuneration of general practitioners was disproportionately low when compared with the pay of dentists and opticians he refused to accept that this was the case, stressing the fact that 52% of the gross earnings of dentists must be regarded as expenses. Yet there is evidence that in Scotland the average net remuneration of the general practitioner there is much less than the average net remuneration of dentists; and when Mr. Bevan went on to observe that dentists worked all kinds of hours he presumably did not wish to leave his audience with the idea that the general practitioner was able to fit his work into a neat timetable beginning at ten in the morning and ending at six in the evening.

In answer to a question about Sir Stafford Cripps's remark in his budget speech this year that a health tax might be necessary, Mr. Bevan said, "If by tax is meant payment by the patient at the moment when the patient needs treatment, we set our faces against it." One of the principal worries in the Service was, he said, over-prescribing. The 14,000 chemists in the scheme had had to deal with 187,000,000 prescriptions, and he appealed to patients not to be importunate, especially in asking for "ordinary" things like aspirins and cotton-wool. Yet when he was asked later whether it might not be a good thing if the patient were to make a nominal payment he replied that a nominal payment would not be a deterrent, and if it were large enough to be a deterrent it might prevent people from seeking medical help when needed. This, we suggest, does not allow for the fact that if the patient were to make a small payment, whether on the occasion of the first consultation with the doctor or for a prescription, he would be encouraged to use the Service with a greater sense of responsibility. It seems likely that sooner or later Mr. Bevan or one of his successors will have to overcome the Minister's desire to be a public benefactor, and will have to introduce some scheme of payment which will be a greater deterrent than mere exhortation to the public to be careful about spending money provided almost entirely out of the taxpayer's pocket.

There seemed to be some contradiction in two statements Mr. Bevan made. He said: "We must rest upon the principle that the doctor must be free to prescribe what he considers to be necessary for the care and welfare of his patient." Later on he remarked that "he had asked a small specialist committee to draw up a list of drugs which the general practitioner can prescribe which are adequate for the purpose and outside which the general practitioner need not go except in special cases." It is not clear whether he was contemplating an alternative to the present formulary, but in any case the implication is that the special cases referred to will have to be defined. In that event the freedom to prescribe will be limited.

When someone asked Mr. Bevan why private patients should not be provided with free drugs he made the usual reply that prescription is part of the service of the general practitioner and the two cannot be separated. When he went on to say that the individual citizen in Britain does not pay a weekly contribution to the

National Health Service, and if he did not enter it was not prevented from receiving something for which he was paying, he was wrong in his facts. Something like nine-tenths of the cost of the Service is borne by the taxpayer, and if he is prevented from accepting part of the benefit of the Service then he is prevented from receiving something for which he has paid. Mr. Bevan, incidentally, asked those journalists present to correct the prevalent misconception that the whole of the weekly contribution to National Insurance was a contribution to the Health Service. There had, he said, been in fact no increase in insurance contributions in respect of the National Health Service, and complained of the confusion that had arisen. This confusion was widely spread by those national newspapers which supported Mr. Bevan during the controversy over the National Health Service, and he himself now seems to wish to create a further misconception by saying that the private patient not allowed to receive drugs free of charge "is not desisting from receiving something for which he is paying."

All the financial implications of the National Health Service must be of much concern to the medical profession. In the national interest some limit must be set to the drain on the exchequer from the mounting cost of the N.H.S. If the finances of the scheme continue to get out of hand the possibilities of properly remunerating general practitioners must diminish. Some idea of the great increase there will be in hospital expenditure may be gained from Mr. Bevan's statement that there was need for 40,000 to 50,000 more nurses. He admitted that in some parts of the country the general practitioners are overworked, and at the same time praised "the thousands of devoted professional men and women who go about their work in a proper fashion." Yet he omitted to say—and unfortunately no question elicited a reply from him on this point—that general practitioners as a whole are working with a strong sense of justifiable grievance about their terms and conditions of work. Until these grievances are removed no Minister of Health will be able to say that the National Health Service is or has been a success. Referring to abuses in the Service, Mr. Bevan said that it was "a prerequisite of human behaviour that a human being should be allowed to behave, and what we must do is to give people the opportunity of behaving, study their behaviour, and make whatever corrections are necessary afterwards." This will certainly be the considered attitude of the medical profession in relation to the Minister of Health.

The Minister's speech is reported in this week's *Supplement*, and there is space here to comment on only some of his observations, many of which displayed his interest in and awareness of some of the problems that concern medicine. He showed, for example, a sympathetic grasp of the difficult question of providing for the chronic sick and the old people who require careful nursing. The problem of the chronic sick could not be tackled by providing expensive beds in hospital needed for the acute sick. Once provision had been made for this growing section of the community it should be necessary only in the last resort to use beds in "acute" hospitals for those nearing the end of their days. Mr. Bevan, too, saw the opportunities for research when on an agreed terminology medical men would be able to supply material for statistical analysis and so open up further possibilities for research, and he gave as an instance rheumatism, pointing out how valuable it would be to know in what age groups, occupations, and parts of the country the various forms of rheumatism occurred.

In his Press conference there were at least two Mr. Bevans speaking—first, the politician skilful in evading an awkward question or giving an answer which really demanded a further question to nail him down; second, the man who has a remarkable grasp of the complexities of the National Health Service and combines with this a desire to provide the people of Britain with every facility for improving and maintaining health. When the organized medical profession negotiates with the Minister of Health it prefers to meet him in the latter role.

PREGNANEDIOL ASSAYS

Many recent advances in the practice of obstetrics and gynaecology are the result of endocrine research. The need for the clinician to keep abreast of the main advances in this field and to understand the principles underlying hormone assays and biological tests was pointed out recently in this *Journal* by de Watteville and his colleagues.[1] They drew attention to the limitations as well as to the advantages of such procedures and emphasized the need for caution in the interpretation of the results. The value of estimating the output of pregnanediol, the chief but not the only urinary metabolite of progesterone, was discussed at the recent Twelfth British Congress of Obstetrics and Gynaecology, the final conclusion being that it is probably too early to assess its usefulness. Dr. G. I. M. Swyer's

[1] *British Medical Journal*, 1949, **2**, 352.
[2] Ibid., 1948, **1**, 683.
[3] White, P., and Hunt, H., *J. Amer. med. Ass.*, 1940, **115**, 2039.
[4] *J. clin. Endocrinol.*, 1941, **1**, 461.
[5] *Amer. J. Obstet. Gynec.*, 1946, **51**, 403.
[6] Christie Brown, R., *British Medical Journal*, 1948, **2**, 851.
[7] *Amer. J. Obstet Gynec.*, 1947, **1**, 627.
[8] *Introductory Papers*, Twelfth British Congress of Obstetrics and Gynaecology, 1949, p. 51.

contribution to the discussion appears in this issue of the *Journal*.

As a diagnostic test for pregnancy pregnanediol assay has been tried and generally found wanting. False positive readings can occur in the presence of delayed ovulation, corpus luteum cysts, and over-activity of the adrenal cortex; and false negative readings are so frequent as to make the test much less reliable than many of the gonadotropin tests, at least one of which can be as rapidly performed. It is often because of vaginal bleeding after one or two missed periods that the practitioner asks for a pregnancy diagnosis test, and Bender[2] claims that in 36% of cases of true threatened abortion the pregnanediol test is negative when the gonadotropin test is positive. If abortion does threaten, a low pregnanediol excretion is held to give warning of an unfavourable outcome, but Bender points out that it is also an indication to administer progesterone with a reasonable prospect of averting miscarriage unless the condition is already irreversible. If, on the other hand, the pregnanediol excretion is normal in such cases the administration of progesterone may accelerate abortion. Pregnanediol determinations indicate that repeated progesterone failure is not a major cause of habitual abortion, and progesterone should be withheld unless the assay gives a low reading. The rate of foetal loss and of maternal toxaemia is abnormally high in pregnant diabetic women in whom there is evidence of maternal hormonal imbalance, including a low pregnanediol excretion,[3] and the results of treatment with oestrogen and progesterone, though not conclusive, are encouraging. Smith[4] claims that a fall in pregnanediol output precedes the development of clinical signs of toxaemia of pregnancy, but this has not been finally confirmed. Moreover, initial hopes, mentioned by Dr. Swyer, that the combination of a gonadotropin test positive in dilution with a negative pregnanediol test would be diagnostic of hydatidiform mole have also failed to be realized. Finally, the work of Lyon[5] has suggested that once the decline in the output of pregnanediol which sets in about ten days before labour has begun the threshold of labour has been reached, and the induction of labour may then be attempted with confidence. Dr. Swyer's findings in this respect are equivocal, and at present few obstetricians will place reliance on hormone assay when deciding whether conditions are suitable for induction.

In the non-pregnant woman pregnanediol determinations are more laborious and time-consuming because of the small amounts excreted. For the diagnosis of the occurrence and time of ovulation they have been superseded by basal body-temperature charts. But where it is suspected that childlessness may be due not to failure of conception but to failure of nidation because of poor progestational response in the uterus[6] there may be a place for pregnanediol assays, for if the total amount excreted is small or limited to a few days the infertility may be due to a defective luteal phase and substitutional therapy with progesterone might be helpful. Functional uterine haemorrhage is another disorder in which pregnanediol estimations might provide useful information. McKelvey and Samuels[7] have shown that when the bleeding is characterized by asynchronous shedding of the endometrium there is an abnormal persistence of pregnanediol in the urine during the bleeding phase. Anovular haemorrhage, on the other hand, as in metropathia haemorrhagica, might be recognized by the pregnanediol content of the urine being very low or *nil* over a period of weeks. Most cases are diagnosed by curettage, but in young girls there is a proper reluctance to perform an operation, and these assays may then have some value. The time for this, however, except as an experimental study, has not yet arrived, and indeed the practical value of pregnanediol tests is clearly strictly limited. Dr. Swyer goes so far as to conclude that they are of such little help to the clinician that every effort should be made to find a method of estimating the level of progesterone in the blood, despite the fact that as a rule the concentration of hormones and their products is lower in the blood than in the urine.

The theoretical basis of pregnanediol assays lies in clinical observations that the amount in the urine, broadly speaking, reflects progesterone activity in the body. But Marrian,[8] a leading authority in this field, now casts doubts on the validity of this basic assumption. Despite this, however, he acknowledges that there is a considerable weight of evidence that pregnanediol determinations may be useful clinically, and therefore he urges clinicians to continue to test the results without prejudice and biochemists to improve still further the methods of assay. The time has certainly not yet come when pregnanediol estimations can be regarded as a useful routine laboratory procedure for general application, but it is to be hoped that a few centres, well equipped for accurate and controlled studies, will continue to work on this problem.

CHANGES IN USE OF HOSPITALS

An important statement from the Ministry of Health published this week in the *Supplement* comments on the procedure to be adopted when a hospital board wants to change the use to which a hospital has been put. Powers are delegated to the board subject to the Minister's direction, and "he cannot ignore representations made to him by members of the public and of the profession." If a

board wishes to change the use of a hospital, "he may feel bound at any time to call upon a board to report to him their reasons for adopting their new policy." The circular emphasizes that boards should consider the possible loss of service to patients and disturbance of medical staff. Where a hospital of long-standing repute is concerned, the board is required to give the medical staff an opportunity of having its views considered, orally if possible, by the board or its planning committee. In some cases an open meeting may be desirable where members of the public can express their views.

The circular points out that local loyalty is of great importance, and the Minister asks boards to make sure that they do not deprive patients of hospitals where general practitioners of the neighbourhood may treat them. The Minister considers that it is "very valuable for the general practitioner service of the district when the family doctor has access to beds where patients . . . can be in his charge and he knows he can readily call upon the services of a consultant for a second opinion." The Minister emphasizes that cottage hospitals must not be regarded merely as buildings providing additional accommodation for relieving pressure on beds at the district general hospital. This circular should have a salutary effect in some regions where boards are proposing to change the use of hospitals. In particular, we may hope that the decisions on the future of the Lock and Paddington Green Hospitals will be reversed.

PARENTERAL FEEDING

In recent years much interest has been shown in the use of amino-acids and protein hydrolysates for feeding in certain categories of illness in which the patient cannot be fed adequately by mouth. The indications for parenteral feeding are inability to ingest, digest, or absorb sufficient quantities of food over such a period of time that convalescence is jeopardized and, perhaps, the chance of survival prejudiced. The most recent information on the subject of amino-acids and protein hydrolysates was discussed at the end of last month in London at a symposium held by the Food Group of the Society of Chemical Industry, and a report of some of the papers which were read appears elsewhere in this issue. The available evidence indicates that nitrogen equilibrium can be attained and the protein needed by normal adult animals, including man, can apparently be supplied, provided energy requirements are met, by injecting into a vein properly prepared hydrolysates of biologically efficient proteins or by the provision of the essential amino-acids and an additional nitrogen source such as glycine. In general, the experiments have not been continued long enough to show that all the physiological requirements of the adult organism for nitrogen can thereby be met. There is no evidence that intravenous administration is nutritionally superior to the oral route if the latter is practicable, but protein hydrolysates are disagreeable to take by mouth. It is seldom possible to give regular intravenous injections of more than the equivalent of 75 g. of protein and 300 to 400 g. of glucose daily. If hydrolysates are injected too quickly nausea and sometimes vomiting may lead to less efficient use of the constituent amino-acids and peptides. There is no definite evidence that the administration of hydrolysates or amino-acid mixtures orally or by tube into the alimentary canal has any special value. Intact food protein by mouth is much more satisfactory.

The reason for employing amino-acid mixtures parenterally in place of, or along with, intact blood proteins in certain conditions is said to be based more on the necessity to sustain liver function and encourage a more vigorous nitrogen turnover than to build up a store of protein. To save body protein it may be wise to include all the amino-acids rather than to rely on the essential amino-acids plus glycine. Because of the difficulty of infusing sufficient protein and energy in the infusion fluid it is generally agreed that it is not possible to make good the requirements of the protein-depleted organism entirely by intravenous injection. It is not wise to inject fluid containing more than 5% of hydrolysate and 5% of glucose, but mixtures containing 8% of pure amino-acids can be given. Even with these concentrations it may take some four hours to inject 2,000 ml., and the patient may be very uncomfortable and demand rest. Some patients suffer actual distress.

Calorie requirements are inadequately met by these intravenous methods of feeding, and the recent work of Rose[1] indicates that with amino-acid mixtures or protein hydrolysates the deficiency is greater than would be expected with the equivalent of intact protein. It is held by some that for short periods of time the glucose intake can be safely limited to 100 g., the rest of the energy needs being met from the adipose tissue. The use of a stable finely divided emulsion of fat with a particle size of not more than two microns, such as that used by Geyer and his colleagues,[2] may prove to be a helpful method of meeting calorie requirements, but more corroborative evidence is required.

ERYTHEMA NODOSUM AND NODAL ERYTHEMA

The importance of tuberculosis in the aetiology of erythema nodosum is referred to in a paper by Dr. S. A. Doxiadis which appears elsewhere in this issue. Some aspects of the problem, however, remain obscure. It is possible that confusion results from casual clinical observation. The true eruption has a characteristic colour both in active and fading stages. The size and conformation of the lesions, the location, and the presence of tenderness and pain with pyrexia are distinctive, and if these features are absent it is doubtful if the diagnosis of erythema nodosum should be made. It was these characteristics which lent some support to the conception of a specific infective fever—nodal fever—now abandoned by most experienced physicians. A nodal erythema may accompany the eruption of a toxic erythema multiforme or may follow the administration of sulphonamides: it is sometimes seen in sarcoidosis and in other conditions, but it may be confusing the issue to regard such eruptions as erythema nodosum when they lack many of the distinctive features of that entity.

[1] *Fed. Proc.*, 1949, **8**, 546.
[2] *J. Lab. clin. Med.*, 1948, **33**, 153.

Erythema nodosum, in its classical form, commonly accompanies a recent infection, such as tuberculosis in the young—in which a primary lesion in the lung with unilateral hilar-node enlargement may recall the early phases of a syphilitic infection. The typical eruption following a streptococcal infection of the throat possesses the same features. While these are the commonest provocative causes in this country the condition is occasionally seen in association with deep-seated ringworm or with gonococcal, meningococcal, syphilitic, or other infections. The causative infections vary in different countries, but it seems that the typical attack of erythema nodosum indicates a peculiar and personal response to the presence in the skin of organisms derived through the blood stream from a recent primary focus of infection elsewhere. It is not merely a reaction to toxic products. To justify the analogy with syphilis erythema nodosum ordinarily should not recur. When it does recur it is generally in association with streptococcal infections of the throat, in which the immunity may be assumed to be only transient. Even so, much remains to be clarified. In chronic meningococcal septicaemia the eruption, characteristic in other respects, consists of small lesions scattered profusely over the limbs instead of a few large nummular lesions; it may continue to wax and wane over a period of months, suggesting the presence of an unusual static phase of sensitivity in the tissues. Whatever the explanation may be of the puzzling features of erythema nodosum, it is certainly desirable when the typical signs are present to seek for a causal organism, if necessary in the blood stream or in the skin lesions themselves. In this country care must be taken to exclude tuberculosis, especially in the young, by immediate overhaul and follow-up of the patient and by investigation of all contacts.

BEGINNING MEDICINE

About 2,500 students in Britain have now set off on the long road to a career that probably offers more diversity of interest than any other, a career, too, that is unlikely ever to be overcast by the shadow of unemployment, though in its initial stages the National Health Service has created difficulties rather than solved them for the man wanting to settle in clinical practice. All acknowledge that a wide general education is desirable for a medical student, and the foundations for this must be laid during the school years. But once embarked on the study of medicine few students find the time or energy to see far beyond the heavy textbooks that burden their knees for many years; and it must be confessed that of those who do some turn out to be interesting companions rather than pioneers in research. As Professor E. C. Dodds said[1] at the annual dinner of the Middlesex Hospital Medical School, the London schools are too narrow in their education, and we welcome his claim that the Middlesex School aims at keeping the basis of education as broad as possible.

The complement of a broad education is to be found in research, and Sir H. Cairns, in his inaugural address[2] at King's College, suggested that "nearly every young doctor should try his hand at one investigation . . . otherwise he will not find out what he is good for, nor will he appreciate the difficulties and labours involved in discovering new things." Every case contains some new thing that must be discovered, and if a knowledge of the textbooks helps the young doctor to clarify the patient's disorder quickly a training in research, even though slight, will make him more sensitive to the details peculiar to the patient that defy classification. Moreover, it encourages an inquiring habit of mind, and he learns that, in the words of Clement of Alexandria,[3] "the beginning of truth is to wonder at things."

Certainly the antithesis of this attitude is thinking "in moaning terms of what terrible conditions you are living under," against which Lord Bruce[4] warned the students when he opened the new term at University College Hospital. He emphasized the need for hard work, and medical students will not fail to appreciate the point when they examine the curriculum. He also adumbrated—as did Sir Hugh Cairns—a life of service rather than of place-seeking—an ideal readily accepted by young people, but which becomes more difficult to live up to as the passing years bring increasing opportunity to depart from it. The great fear is that the National Health Service, in spite of its name and aim, may not encourage the doctor to give of his best in service to the sick; in the words of Principal T. M. Taylor[5] when he addressed graduates at Aberdeen recently, "It will be an ill day for the community when the general practitioner degenerates into a filler of forms or an automatic machine dispensing chemical panaceas." Five or six years will pass before students now starting work seek in the practice of medicine that full and happy life that Sir Hugh Cairns wished them. Within that time the National Health Service will be over the experimental stage and, it is hoped, be better adapted to satisfying their aspirations.

REFRESHER COURSE FOR GENERAL PRACTITIONERS

In this issue of the *Journal* we publish the first of a series of articles which will appear week by week under the heading of "Refresher Course for General Practitioners." Before the war we used to publish each week a special article of this nature for the general practitioner, but because of shortage of paper we had to discontinue this feature in 1939 until now. More paper has been available since the beginning of July, and it is hoped that no further restrictions will increase our difficulties in keeping a wide variety of readers informed on matters of special interest to them. "Any Questions?" was started in 1943 as an attempt to meet the need of the general practitioner for information on problems which concerned him in his daily work. It is hoped that this section of the *Journal*, together with the new Refresher Course, will continually revise for the general practitioner what is old and keep him fully acquainted with what is new in a manner that will be of practical use. We would welcome suggestions from readers for subjects that might be considered in the Refresher Course articles.

[1] *British Medical Journal*, October 8, p. 811.
[2] Ibid., October 8, p. 805.
[3] *Stromateis*, quoted in *The Apocryphal New Testament*, O.U.P., 1924.
[4] *Daily Telegraph*, October 5.
[5] *Scotsman*, September 9.

REFRESHER COURSE FOR GENERAL PRACTITIONERS

THE ACUTE THROAT

BY

T. ANDERSON, M.D., F.R.F.P.S., F.R.C.P.Ed.

Lecturer in Infectious Diseases, Glasgow University

The complaint of "a sore throat" must be one of the commonest made to the doctor, and as the condition sometimes calls for urgent treatment the correct diagnosis is of some importance. Although the initial complaint focuses attention upon the throat it is necessary to remember two fundamental points: first, a throat infection may exist without sufficient pain to draw notice to its presence, which bears out the old clinical rule that examination of a patient—particularly a child—is not complete until the throat has been inspected; secondly, it should never be forgotten that the throat inflammation may be the local manifestation of some general disease.

Examination of the Throat

The examination of the throat is such a simple procedure that a description of the necessary manipulations is often taken for granted. Yet to obtain a proper inspection in a writhing youngster calls for tolerance and persistence on the part of the doctor. With patience and persuasion the co-operation of the child will often be fully attained, and where this course is possible it is much to be preferred. No attempt should be made to use force. The following points may be of assistance in difficult circumstances.

(1) *Holding the Child.*—When there is complete refusal to co-operate it will be necessary to pinion the child. The best method is to bring both arms across the chest and for an assistant to hold them there by catching both wrists in one hand. The assistant's other hand should hold the head firmly on the bed by placing the open palm across the forehead, the thumb to one side and the fingers to the other. In such a way the child may be held firmly and painlessly.

(2) *Opening the Mouth.*—Sometimes an unwilling child will hold the jaw tightly clenched. The spatula should then be inserted along the left-hand side of the mouth between the teeth and the buccal mucosa. Firm pressure inwards as far back as possible on the lateral aspect of the alveolar margin will usually result in the mouth being opened. The spatula can then be rapidly turned flat and passed on to the tongue.

(3) *Position of the Spatula.*—The spatula should be passed far enough into the mouth for the distal end to cover the posterior third of the tongue. Pressure should be downwards and forwards to enable a full view to be obtained of the fauces without forcing the tongue back into the throat, which not only blocks the airway but causes the child to "gag."

Diagnostic Points

When examining the throat the doctor must ask himself the following questions:

(1) *Is the Throat Acutely Inflamed?*—The soft palate, faucial pillars, tonsils, and pharyngeal walls should be carefully inspected for redness and oedema. The lesion may vary from a slight reddening of the palatal fringe, uvula, and anterior pillars to oedema so gross that the swollen uvula, palate, and tonsils almost close the faucial airway.

(2) *Is there an Inflammatory Exudate?*—This may be unilateral or bilateral, and three stages in its formation may be recognized. First comes the appearance of numerous discrete follicular flecks; secondly, there is a confluent, soft, loosely attached and rather pultaceous exudate; and, thirdly, one sees a confluent, firm, leathery membrane which is more or less firmly attached to the subjacent mucosa. Note that exudate is usually confined to the tonsillar surfaces, but membrane may extend on to the fauces, soft palate, or pharyngeal wall.

(3) *Is the Lesion Raised?*—When exudate or membrane is present its level relevant to the adjacent mucosa must be noted. The doctor must satisfy himself whether it is superimposed upon the mucosa or level with the adjacent surface, as if forming the base of a shallow ulcer.

(4) *Is the Membrane Discrete?*—It may be one continuous piece, or made up of numerous solitary areas with intervening normal mucosa.

The causes of a sore throat may be grouped under three broad headings—local virus infections, local bacterial infections, and general diseases.

Virus and Bacterial Infections

Influenza may start with a complaint of sore throat. In such cases the throat often shows little abnormality apart from some enlargement of the solitary follicles on the pharyngeal wall. There seems little doubt, however, that an upper respiratory virus infection can produce a generally inflamed throat with or without tonsillar exudate exactly similar in appearance to that of an acute bacterial infection.

Coccal Infections.—It is impossible to differentiate clinically between the various acute coccal infections. In general *Str. pyogenes* produces a severely inflamed and oedematous throat usually of sudden onset and associated with such great pain that swallowing is exquisitely sore. A tonsillar exudate is common with streptococcus, pneumococcus, or staphylococcus infections. This exudate may become confluent and closely simulate a false membrane, but it is more friable and white or yellow in colour. The associated lymph glands are enlarged and tender but remain discrete. In such cases the ear drums should always be examined. The drum-head may show a diffuse pinkness and slight lack of lustre that suggests a coccal tonsillo-pharyngitis.

Scarlet Fever.—A sore throat precedes the onset of scarlet fever, and the initial rash is often seen on the soft-palate, giving it a speckled appearance. The skin rash will usually confirm the diagnosis within 18–24 hours.

Pharyngeal Abscesses.—A peritonsillar abscess may develop on top of a pre-existing acute tonsillitis. The unilateral, tense swelling of the fauces and soft palate, pushing tonsil and uvula to the opposite side, is easily recognized, and the intense pain is a characteristic feature. Retropharyngeal abscess can be difficult to diagnose,

particularly in young children, because of the filling of the pharynx with mucus as a result of the difficulty in swallowing. The swelling produces a curious choking stridor which may be mistaken for laryngeal obstruction, but the latter produces a much "drier" stridulus with harsh cough. The fauces may show little inflammation in such cases, and should the character of the respiration have aroused suspicion there is only one course of action—persistence in obtaining a good view of the pharyngeal wall.

Diphtheria

A few years ago diphtheria would have taken first place in any consideration of the differential diagnosis of a sore throat. As a result of a reduction in incidence, largely due to active immunization, the clinician need not to-day regard it as occupying so high a place on the list. But it is well to keep two considerations in mind. First, in face of an appearance which suggests diphtheria a history of immunization should never encourage the practitioner to consider the diagnosis impossible. Secondly, it must be remembered that in the "immunized" subject a diphtheritic infection may produce an appearance indistinguishable from that of follicular tonsillitis. Typically, infection of a susceptible person with *C. diphtheriae* has an insidious onset and produces a mildly inflamed throat; the greyish membrane is "all of a piece" and often shows a slightly curled edge which may spread on to soft palate, faucial pillars, or pharyngeal wall when diagnosis is delayed. In general, the inflammatory reaction is limited to a zone surrounding the membrane and the diffuse bright redness characteristic of a streptococcal infection is seen less commonly. Pain is not a feature—indeed, it is often surprising to find how little pain may be associated with an easily recognized, severe diphtheria. Adenitis of the tonsillar glands, so often referred to in textbooks, is the mark of the severe or late case and is of little assistance in making an early diagnosis.

The most confusing appearance is produced by a severe *gravis* diphtheritic infection. The inflammation is intense and the soft palate and anterior aspect of the faucial pillars may be very oedematous and covered with a thin glairy mucus which is not unlike white of egg. This is, in fact, early membrane. The typical membrane may be slight or absent and the condition carelessly regarded as a quinsy. When diphtheria is epidemic the clinician should never hastily use a knife on what seems an acute peritonsillar abscess, for if the lesion is in reality diphtheritic incision greatly worsens the prognosis.

The diagnosis of diphtheria is never easy and even the expert can define no absolute diagnostic criteria. It should be more widely appreciated that modern diphtheria antitoxin is a highly refined and concentrated product, 8,000 units of which can be obtained in a 2 ml. syringe. When the clinician is in any doubt a dose of this magnitude is a safe procedure and will be adequate for most early cases. Serum reactions are now so rare as to be negligible.

Vincent's Angina.—This condition, like diphtheria, has an insidious onset, and as a rule produces little rise in temperature. The throat may simulate diphtheria in that the slough covering the ulcers suggests membrane formation. It will be observed, however, that the membrane is on a level with the normal mucosa and that it makes up several discrete, linear lesions separated by more or less normal mucosa. Although ulceration is seen in rare cases of diphtheria the lesion is continuous and does not consist of individual ulcers. In Vincent's angina the whole mouth is often unhealthy and the gums are inflamed and swollen—a further aid to diagnosis.

Sore Throats in Schools

In closed communities such as boarding schools, outbreaks of acute tonsillitis are most frequently streptococcal in origin. The cultures from the initial cases will usually decide which organism is responsible, and as a rule the swabs of throat and nose produce a heavy, almost pure, culture. Early diagnosis and isolation of those infected are the measures most likely to limit spread, but the high carrier rate which often accompanies such an outbreak may entail the isolation of a large proportion of the individuals. To begin with, all the residents must be subjected to a clinical examination at which particular attention is paid to ears, throat, and nose for the presence of otorrhoea, enlargement or irregularity of tonsils, or rhinitis. Those who show such abnormalities should have cultures taken from nose and throat and should be separated from the others; for it is this group which usually contains the carriers. The remainder should be inspected daily for a period of seven days and any individual showing signs of upper respiratory tract infection isolated at once. When cases continue to crop up among those who showed no abnormality of throat, nose, or ear two possibilities should be considered: first, that the epidemic is food- or milk-borne, and, secondly, that there is an unsuspected carrier remaining among the apparently healthy residents. In connexion with the latter possibility it is important to remember that the nasal carrier is the more dangerous.

When tracing the source of an epidemic which may involve a considerable number of persons the doctor should make early contact with the local medical officer of health and the nearest unit of the Public Health Laboratory Service. Precise knowledge of the organism involved is essential for any useful epidemiological work. For example, by determination of the serological type in streptococcal outbreaks it is possible to make more accurate decisions regarding the importance of a carrier or to assess the significance of milk or food in the spread of infections. Early consultation with the bacteriologist will ensure not only that he receives the right kind of specimens but also that he is able to proceed with the further definition of the pathogen involved.

Specific prophylaxis is only practicable in outbreaks of diphtheria, when combined active and passive immunization should be started. This consists of the injection of 500–1,000 units of diphtheria antitoxin into one arm and 0.5 ml. of A.P.T. (alum precipitated toxoid) into the other. Six to eight weeks later a second injection of 0.5 ml. of A.P.T. is given. Prophylaxis of streptococcal infections by the administration of sulphonamides is not advisable as a routine measure.

General Infections

Glandular Fever.—The anginose form of infectious mononucleosis produces a throat which may be indistinguishable from an acute coccal infection—indeed, the secondary invader is often a *Str. pyogenes*. Glandular fever is a systemic virus infection. Generalized lymphoplasia and splenomegaly will probably be present, but the diagnosis may be suggested by the sore throat suggestive of streptococcal tonsillitis appearing as a secondary manifestation after a few days of general malaise. In the usual streptococcal infection the sore throat is the first manifestation of an acute illness. There is little doubt that infectious mononucleosis now occurs more frequently than it did in the past. Accurate diagnosis depends upon the differential white cell count, which shows a mononuclear

leucocytosis and the characteristic atypical cells, and the demonstration of heterophile antibody in the patient's serum by the Paul–Bunnell reaction. This reaction is variable in the time of its occurrence and often becomes positive for the first time late in the illness. A titre of 1/64 is significant. Should the patient have received horse serum in the form of an antitoxin the bacteriologist must be informed, so that he may take steps to eliminate the resulting false-positive reaction.

Agranulocytic Angina.—The throat may show ulceration and membrane formation. There is, however, a characteristic lack of inflammatory reaction in contrast to the apparent acuteness of the lesion, and the soft palate, uvula, and fauces look pallid, soft, and jelly-like. The lesion is more frequently seen in adults; and a history will often be obtained of the habitual use of a drug containing the benzene ring. The amidopyrine group and, rather infrequently, the sulphonamides constitute the commonest aetiological agents. Diagnosis depends on lack of polymorphs seen on a carefully taken blood film. The film should preferably be made on cover slips to secure an even distribution of the white cells. If it is taken on a slide the most careful scrutiny should be made along the edges and at the end of the smear, for it is here that the polymorphs will usually be found.

Toxic Drugs.—Whether agranulocytosis is in fact a form of acute sensitization or not is still uncertain, but there is no doubt that an ulcerative stomatitis and pharyngitis without agranulocytosis can occur as part of a drug sensitization. The whole mouth is inflamed in this condition and as a rule there is some confirmatory evidence such as a rash. It is important to appreciate that the individual who has been sensitized to one drug is the more easily sensitized to others, and care should be exercised in the use of forms of therapy involving sensitizing drugs, such as aspirin and the sulphonamides.

Other Conditions.—Acute leukaemia sometimes presents for the first time as an acute ulcerative tonsillitis. The child—for it is more frequently seen in childhood—usually appears ill and anaemic. There may be petechial skin haemorrhages, the spleen is often enlarged, and sternal tenderness is usual. Diagnosis can only be made after a careful examination of the blood.

Finally, in the adult, secondary syphilis should always be borne in mind as a cause of ulcerative tonsillo-pharyngitis. The presence of a typical rash may give a pointer to the correct diagnosis, but failure to respond to any form of treatment is often the first feature to make the clinician think twice about the diagnosis. Toxaemia usually appears mild in contrast to the severity of the local lesion. The Wassermann reaction will confirm the diagnosis.

Bacteriological Procedures

In the past, the focus of attention upon diphtheria resulted in the clinician tending to seek bacteriological assistance only when this diagnosis was under consideration. A carefully taken swab from the tonsillar surfaces, however, is of value in all throat infections and is particularly desirable in severe cases because of the guidance it may give in planning treatment. The swab must be taken before any form of chemotherapy is used. Most bacteriologists include a direct film in their examination of the throat swab, as well as culture on blood agar, Loeffler's slope, and a special medium to differentiate the organisms of diphtheria. The report may therefore supply valuable information in regard not only to diagnosis but also to prognosis.

Treatment

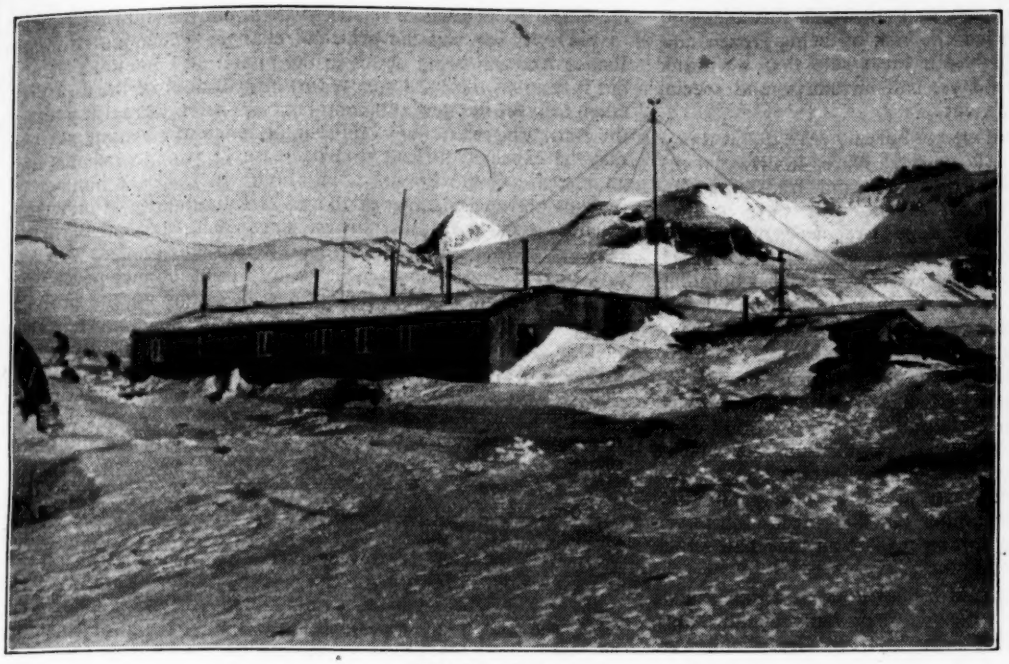
Antitoxin.—Although in many cases treatment will be guided by the results of the bacteriological examination, it is often necessary (and in a suspected case of diphtheria essential) to start treatment before the results of such examination are known. The dose of diphtheria antitoxin ranges from 5,000 to 100,000 units. Where the disease is suspected an intramuscular dose of 8,000 units will suffice. For the late, severe case when hospital admission cannot be immediately secured a dose of the order of 50,000 units will be required, and in such an event intravenous administration is particularly desirable. Such cases are best treated in hospital, however, and the practitioner will find that most fever hospitals are anxious to admit them even when the diagnosis is unconfirmed or in doubt.

Penicillin.—For the coccal infections and for Vincent's angina penicillin is the treatment of choice. It should be realized that the need is to secure an adequate local concentration of the antibiotic. The condition must not be thought of as a mere surface infection. Local therapy by lozenges and so forth is therefore completely inadequate and systemic administration in high dosage is indicated. If the aqueous solution is used a four-hourly dose of 100,000 units should be injected intramuscularly: procaine penicillin may be employed to advantage here, and two or three injections of 500,000 units during the first 24 hours may be followed by a lower dosage for the remainder of the time. For all throat infections due to susceptible organisms treatment must be continued for seven days to secure the best results.

Although there is no specific treatment for infectious mononucleosis the throat infection is usually due to either *Str. pyogenes* or Vincent's infection, and penicillin will prove effective. In agranulocytic angina, also, the administration of penicillin has greatly improved the outlook. Pentnucleotide should be injected intramuscularly. During the first 24 hours three or four injections of 5–10 ml. may be given, and thereafter the dosage will depend on clinical response. The administration of the antihistamine drugs might be considered, but the results have not been encouraging. In severe cases repeated small blood transfusions are valuable. The diet should be plain and contain no flavourings or adulterants, and care should be taken to avoid the use of any chemical which might have a sensitizing action.

Sulphonamides.—The administration of sulphonamides has been intentionally omitted from the treatment of the acute throat. The efficacy of these drugs has never been convincingly demonstrated in such conditions. Since they are undoubtedly toxic materials, carrying appreciable risks of sensitization, their administration is inadvisable, and in certain conditions may even be dangerous.

Finally, it must be pointed out that many mild throat infections clear rapidly and effectively without specific treatment. Gargling is so frequently indulged in by the patient before seeking advice that its continuation may be advised for its effect in cleansing the mouth. For those adults who can gargle, warm water with glycerin of thymol may also prove soothing to the throat. When pain is more severe the application of poultices to the neck, inhalations of friar's balsam, and, of particular value, the administration of aspirin powder, which is allowed to melt slowly in the mouth before swallowing—such measures are often adequate to secure rapid relief. The hasty rush for penicillin as a panacea for all cases is to be deprecated. It may do the patient little harm, but it can induce in the physician an easy optimism which may eventually cloud his whole judgment.



The base hut.
(Photograph reproduced by permission of the Colonial Office.)

THE FALKLAND ISLANDS DEPENDENCIES SURVEY

BY

J. M. ROBERTS, M.B., B.Chir.

In 1943 the British Government decided to dispatch an expedition to the Falkland Islands Dependencies in order to maintain British sovereignty, which was challenged by Argentina and later by Chile. Since that time the continuous occupation of various Antarctic bases has been maintained by a succession of personnel. It was as one of the M.O.s in an annual relief party that I had the good fortune to stay on the Antarctic continent for 14 months. There were 30 in the party, including two M.O.s, one for each of the two large bases. These bases were far apart, the nearest to us being 120 miles away over open sea. Communication between them was maintained by radio, as it was impossible to reach another base except by the relief ship or by a sledge journey of 800 miles (1,300 km.) over unknown country. This journey was in fact done during the year as part of the survey programme, and it took four men 80 days to complete it.

At the beginning of November, 1946, we left London in a small Newfoundland sealing vessel built entirely of wood and powered by a Diesel motor and auxiliary sails. Our journey out was via Recife, in Brazil, Montevideo, and the Falklands, and it took us six weeks to reach Port Stanley, the capital and only large port. The Falklands are bleak, barren islands without trees, not unlike the Western Isles of Scotland. We arrived on Christmas Eve. Although it was midsummer it was very cold, and it snowed appropriately the following day.

After a fortnight's stay to check stores the parties sailed in two ships, one for the South Shetlands and the other for the South Orkneys. Sailing south-east, we took five days to reach the South Orkneys, where we relieved a party of four who had run a meteorological station for the past year. It was on this part of the trip that we encountered our first icebergs and pack-ice. For the most part the weather was extremely fine, and gave us that remarkably clear visibility characteristic of the polar regions. We could see the mountain peaks of the South Orkneys, over 100 miles (160 km.) away, standing so clearly on the horizon that it was not possible to estimate their distance. After two days in this neighbourhood, where we had our introduction to penguins, seals, whales, and other Antarctic fauna, we sailed south-west for Graham Land.

Our destination was Hope Bay, which lies at the north-east tip of Graham Land, at the foot of a glacier which descends from the inland plateau and down which there blows an almost continuous wind. The hut in which we were to live had been erected two years previously, and was partly buried in the ice. It was large and spacious, with double wooden walls and an aluminium-foil diaphragm between them. This bright surface helped to reflect the heat back into the hut, as well as providing two air pockets in the walls; its insulating value was equivalent to an inch (2.5 cm.) thickness of cork. The average temperature inside the hut for the year was 52° F. (11.1° C.), with a minimum of 32° F. and a maximum of 74° F. (0–23.3° C.), compared with the outside temperatures ranging from −14° F. to 49° F. (−25.5–9.4° C.), with an average of 22° F. (−5.5° C.). Inside the hut there was a large central living-room with small cabins leading off, an arrangement which had the disadvantage of cutting off what light there was in the summer. For nine months the hut was completely buried, however, so we had to use artificial light almost all the time. It has been said that cabins are undesirable for long periods of living in close proximity because men may go into hiding away from their companions. This never happened with us, and it was pleasant to have the little privacy cabins provided. Besides these cabins we had a laboratory and dark-room, a survey office, a kitchen, and a carpenter's shop. Outside there were two additional storage huts for reserve stocks. Lighting was by paraffin lamps and heating by an anthracite stove.

Nine men lived at the base. We had a duty rota, so that we each cooked for one week at a time and did the household chores one day in nine. Few of us had cooked before, but we soon learnt. Our diet was good, though mainly of tinned food. Fresh food consisted of penguins, which when stewed with onions can be very palatable, especially the chicks. Penguin eggs, which were very popular, were collected by the thousand and stored in flour. Shags and other birds were occasionally tried. Seals did not prove a great favourite, probably because they were so greasy. We did a certain amount of fishing through holes in the ice; the fish (*Notothenia*) were small, but very good when fried in butter. For fresh water we used blocks of snow, collected sufficiently far away from the base to be free from contamination due to dog excreta.

We supplemented our diet with 50 mg. of ascorbic acid daily, the tablets being on the table with the cruet. My predecessor had gone for two months without ascorbic acid and had developed early scorbutic signs. During the winter we noticed we were becoming easily fatigued with light work, and so we added vitamin A, 9,000 I.U., and vitamin D, 1,800 I.U., daily for a month; the supplements certainly seemed to have some benefit, although the reason is not entirely clear.

We were issued with ample supplies of tobacco and cigarettes, and all of us became heavy smokers by the end of the year. As with the food, we divided all our stocks in two, so that if we failed to be relieved we should be able to last another 12 months.

There was an issue of rum, whisky, and gin which was adequate for our needs, but beer entailed the risk of being frozen and breaking the containers. We had a local rule that we drank only on Saturday nights, birthdays, half-birthdays, and special feast days, such as midwinter's day.

I have been often asked, Did we get bored? We did at times, but there was plenty of work to do. Three-hourly "met" observations had to be made, recorded, and transmitted by radio. We had the dogs to feed, which meant days of seal-hunting, and our sledges had to be kept in repair. Our stock of books was widely selected, and games such as darts, draughts, and "nine men's morris" were also popular. Against boredom of our companions I think each of us built up his own defence mechanism: there was a strict regulation that stories were not allowed to be repeated more than once a month.

During the year survey parties left the base for long sledge journeys. Usually there were two men to one sledge, which carried their food and tent and was pulled by a team of 13 dogs. The distance covered in a day varied greatly with the type of country and weather encountered, but the average speed was 4 m.p.h. (6.5 km.p.h.). One party travelled nearly 60 miles (95 km.) in 24 hours, while another did 200 yards (180 m.) in the same time, as a blizzard sprang up just as they had struck camp.

Sledge runs were usually made for an hour at a time, as we found the dogs would go better if they had regular stops. These dogs, 40 of which were brought from Greenland, were the best companions one could wish to have. Their social habits made a fascinating study, and, though fierce among themselves at times, they never bit any of our party. From the original 40 they increased their numbers up to 120 by the end of the year.

Throughout the year the general health of the party was excellent, and we were completely free from colds, unlike other expeditions who reported that they caught colds every time they opened fresh bales of clothes which had been left undisturbed from the time they were packed in England. We did get colds when the relief ship arrived, however. We had one or two infected cuts from handling seal blubber, but I do not think these were comparable in severity with the spek finger of the northern sealers. One case did lead to chronic ulceration of the arm and axilla, the pathology of which was uncertain. Frostbite and snowblindness, the two enemies of the polar regions, were never severe, mainly because we took care to avoid them. Carious teeth required frequent attention, which was usually given in the form of a temporary stopping, though occasional extractions were called for. The only major casualty was a man with two slipped intervertebral disks, which kept him in bed for over eight weeks and which it was found necessary to remove on his return home.

THE PRISON POPULATION

ANNUAL REPORT OF THE COMMISSIONERS

The average daily prison population in this country is around 20,000, a considerable increase on the 13,000 of five years ago. Populations of the present order have not been known since 1911. The number of receptions on conviction—which is always greater than the number of different persons received in prisons, since some men after finishing one sentence are sent to prison again in the same year—was 33,566 in 1947. Women account for about one in ten in these totals. Well over half the offences for which persons are received in prison are larceny and burglary and housebreaking. Sexual offences by men accounted for 1,053 receptions in the year under review, and offences of violence, including murder and manslaughter, for 728 receptions of men and 81 of women. About half the male prisoners and 70% of the female prisoners were sentenced for not more than three months.

In the Report of the Prison Commissioners just published[1] the narrative as a whole relates to 1948, but the statistics mainly to 1947. It sets out the principal changes which the Criminal Justice Act will bring about in the prison and Borstal systems, but it reserves until the next report any account of the measures taken to meet the new and complex responsibilities arising under the Act. The restrictions on the imprisonment of young persons may be expected to lead to a decrease of young prisoners and an increase in the Borstal population. In 1947 the number of persons between the ages of 16 and 21 found guilty of indictable offences was 19,331, the lowest since 1940, and of the 2,912 persons in this age group sentenced to imprisonment 790 had not, so far as was known, been guilty of any offence previously.

It is not easy to draw any firm conclusions on the problem of recidivism from the statistics given in this report. They include the numbers of convicted prisoners against whom previous offences were known, but the factors affecting such figures over a long period of years are so many and variable that the Commissioners themselves withhold any comment. Of the convicted prisoners in 1947, 71.5% of the males and 67.5% of the females had previous proved offences. Indeed, 392 men and 43 women had over twenty previous convictions. It should be added that from these figures imprisonment for drunkenness is excluded, the reason being that if it was included it would overweight the figures on the female side. Thus in the year under review 1,115 men and 349 women were imprisoned for drunkenness, but while the first figure represents only 3.7% of the total number of male convicted prisoners the figure for females represents 10%. The numbers imprisoned for drunkenness in 1947 were only about one-fifth of the total for 1938. Comparisons with a much earlier period are vitiated by the fact that not until the Criminal Justice Administration Act, 1914, was time required to be given for the payment of fines, and therefore in earlier years there was a very large transitory prison population.

The Borstal System

The change of name from "Borstal detention" to "Borstal training" is welcomed. The Commissioners point out that Borstal is in the "news" when things go wrong, but good behaviour has no news value. The conduct of the Borstal boy is on the whole satisfactory, and often very good, although it has to be admitted that nearly a thousand boys absconded or attempted to abscond during the year. It is not a simple statistical matter to find out whether Borstal boys make good. From the figures given it appears that more than half those discharged are not re-convicted, but only intensive social research based on personal histories over a long period can show how many of these young men have become useful members of society. The Borstal population consists of about 3,000 boys and rather more than 200 girls.

The most immediate effect of the introduction of the National Health Service was a large increase in the number of prisoners receiving dental and ophthalmic treatment. It has also been possible to arrange in the case of Borstal inmates for operations to be performed at local public hospitals. Arrangements have now been made, and are being extended to all prisons, for cases of venereal disease to be treated by venereologists serving in local clinics. In the case of small prison establishments prisoners are sent to the public clinic as often as may be necessary, and in larger ones venereologists hold their clinics in the prisons. Other National Health Service facilities of which full use has been made are those in connexion with tuberculosis, though in this case the change has been no more than administrative.

This greater use of public services, while it has not lessened the prison medical officer's responsibility for the health of all prisoners in his charge, has to some extent freed him for the undertaking of certain special investigations. The report gives a list of researches which have either been completed or are in progress.

Psychiatric Studies

An investigation is being carried out at Wormwood Scrubs and Wandsworth, in collaboration with members of the Maudsley Hospital staff, on prisoners who are psychopathic personalities and who consent to undergo the tests. The group

[1] *Report of the Commissioners of Prisons and Directors of Convict Prisons for the Year 1948.* Cmd. 7777. London: H.M. Stationery Office. 2s. 6d. net.

is limited to male offenders between 18 and 40 in whom there is no family history of epilepsy. A similar number of offenders whose personalities are regarded as normal are to be used as controls. Research into the endocrinological aspect of cases of psychopathic personality is in progress at Bristol and Leyhill (known in the Press as the "prison without bars"). At Holloway an investigation into the causes of child neglect by women has recently been completed. Studies at Wakefield under the principal medical officer include the whole population of the prison. From the history and the physical and psychiatric examinations and tests a profile is constructed which gives at a glance the principal features in the early home circumstances, the civil state, the criminal career, and the mental condition of each prisoner received. To provide for the psychological treatment of prisoners serving short sentences arrangements are being made for psychiatrists employed by the regional hospital boards to attend wherever possible at the larger local prisons. In selected cases treatment begun while in prison will continue under the same therapist after release. So far it has been possible to give effect to this only in one of the regions. Prisoners treated at local psychiatric centres during their sentences, largely owing to the sharp contrast between the clinic and the prison, rarely avail themselves of whatever arrangements are made for treatment after release. On the other hand, if a prisoner is visited by a therapist in prison the likelihood of his continuing treatment after release is increased.

Prison Medical Officers

The recruitment of medical officers to prisons does not keep pace with the demands of the service. Notwithstanding the increased opportunities for research, the requirements of the Criminal Justice Act, involving a sharp increase in the number of medical reports asked for by the courts, and prolonged investigations in preparing such reports, together with the necessary attendance at court, will add considerably to the prison medical officer's duties. The report states that "there can be little doubt that it will be difficult to maintain the standard of work or embark on further research unless a substantial increase in the rate of recruitment takes place." Prisons, too, are affected by the nursing shortage. The recruitment of female nursing staff to prisons continues to decline, and a return to prison-trained hospital staffs may have to be considered.

AMINO-ACIDS AND PROTEIN HYDROLYSATES

A RECENT SYMPOSIUM

A symposium on "Amino-acids and Protein Hydrolysates" was held in London on September 28–30 by the Food Group of the Society of Chemical Industry. While some of the papers were on the purely chemical and physico-chemical aspects of amino-acid preparation and isolation, several speakers discussed the nutritional and clinical aspects of protein and amino-acid nutrition and metabolism.

In the course of a comprehensive opening address to the conference Professor E. C. DODDS drew attention to the work of Dent and Schilling,[1] who had examined by means of paper chromatography the portal blood and sometimes also the jugular blood and the urine of dogs after the feeding of various proteins such as casein, casein hydrolysate, ground beef, and human serum (the plasma proteins being removed first by ultrafiltration). No peptides had been found in the blood after any of these proteins were fed. After feeding human albumin certain ninhydrin-reacting substances decomposable by hydrolysis were found in the urine. When dog plasma protein was fed to dogs there was no appreciable change in blood amino-acid levels, though the protein disappeared from the gut. It was presumed from this that under the condition of experiment the dog plasma had been absorbed intact. This finding opens up wide and interesting fields of exploration. Dent[2] has also shown in recent studies that in at least five human diseases—namely, acute yellow atrophy of the liver, the Franconi syndrome, cystinuria, phenyl ketonuria, and multiple myelomatosis—urinary amino-acid excretion is abnormal and characteristic of the disease. Professor Dodds referred to the work with isotopic tracers by means of which the rapidity of turnover of the proteins in the liver had been demonstrated: in rats half the protein is degraded and resynthesized within six days.[3] He also described how certain amino-acids had developed into therapeutic agents, two examples of these being methionine and glutamic acid.

Amino-acids as Therapeutic Agents

The importance of methionine in the body depends on two factors: it contains the element sulphur and a labile methyl group. Because of these two characteristics it plays an important part in the detoxication and lipotropic functioning of the liver. Several workers have shown that methionine can apparently improve cirrhotic conditions of the liver.[4–8] There have also been reports on the use of methionine in the treatment of infective hepatitis, but in this condition it has not been found uniformly successful. Methionine has been used successfully in the treatment of a patient with subacute necrosis,[9] and Eddy[10] reported that in trinitrotoluene and carbon tetrachloride poisoning it gave good results. Glutamic acid has been shown by Weil-Malherbe[11] to be of importance in the metabolism of brain tissue. Zimmerman, Burgemeister, and Putman[12] administered glutamic acid to children and adolescents with convulsive disorders, some of whom were also mentally retarded. They found what they considered to be a significant improvement in the results of intelligence tests.

In 1938 Fildes[13] made the interesting observation that indoleacrylic acid inhibited the growth of *Bact. coli*, and subsequent work showed that 4-, 5-, 6-, and 7-methyltryptophans all possessed the power of inhibition.[14] These observations have been extended to other synthetic amino-acids: Beerstecher and Shive[15] found that β-2-thienylalanine was strongly inhibitive, and Elliott, Fuller, and Harington[16] have shown that certain β-derivations of alanine have antibacterial properties. New chemotherapeutic agents may be found by continuing the study of the metabolism of bacteria in the manner that Woods[17] initiated when he discovered that the sulphonamides compete with *p*-aminobenzoic acid for an enzyme system necessary for bacterial growth.

Amino-acids and Cancer

The observation[18] in 1939 that dextro-rotatory glutamic acid (the presently accepted unnatural form) could be isolated from the protein of malignant tumours was contested by Chibnall and his colleagues,[19] but it was reaffirmed this year by Kögl as a result of tracer studies.[20] Professor Dodds pointed out the importance of such an observation as possibly giving a clue to the reason for the independent continuous reproduction of the cancer cell as compared with the self-limiting reproduction of the non-malignant cell. However, it would appear necessary for considerably more positive evidence to be produced before the presence of a dextro-rotatory acid can be regarded as a characteristic of the protein of malignant tissues.

Apart from the part played by individual amino-acids, there is evidence that they form certain conjugates either with other amino-acids or with chemical groups and that these compounds are of special importance in the body—for example, folic acid

1 *Biochem. J.*, 1948, **42**, xxix (proc.).
2 Ibid., 1948, **43**, xlviii (proc.).
3 Shemin, D., and Rittenberg, D., *J. biol. Chem.*, 1944, **153**, 401.
4 György, P., and Goldblatt, H., *J. exp. Med.*, 1942, **75**, 355.
5 Fagin, I. D., and Zinn, F. T., *J. Lab. clin. Med.*, 1942, **27**, 1400.
6 —— Sahyun, M., and Pagel, R. W., ibid., 1943, **28**, 987.
7 Morrison, L. M., *J. Amer. med. Ass.*, 1947, **134**, 673.
8 Beams, A. J., and Endicott, E. T., *Gastroenterology*, 1947, **9**, 718.
9 Ferriman, D. G., Williams, G. E. O., and Cadman, D. S., *Lancet*, 1946, **1**, 958.
10 *Industr. Med.*, 1945, **14**, 283.
11 *Biochem. J.*, 1936, **30**, 665.
12 *Psychosom. Med.*, 1947, **9**, 175.
13 *Biochem J.*, 1938, **32**, 1600.
14 Fildes, P., and Rydon, H. N., *Brit. J. exp. Path.*, 1947, **28**, 211.
15 *J. biol. Chem.*, 1946, **164**, 53.
16 *J. chem Soc.*, 1948, 85.
17 *Brit. J. exp. Path.*, 1940, **21**, 74.
18 Kögl, F., and Erxleben, H., *Hoppe-Seyl. Z.*, 1939, **258**, 57.
19 *Biochem. J.*, 1940, **34**, 285.
20 *Experientia, Basel*, 1949, **5**, 173.
21 *J. Lab. clin. Med.*, 1948, **33**, 153.
22 *Fed. Proc.*, 1949, **8**, 546.
23 *Science*, 1949, **110**, 213.
24 *British Medical Journal*, 1948, **2**, 731.

(pteroylglutamic acid). Synthetic products which are modifications of this amino-acid derivative are being used extensively in the treatment of cancer, and typical examples are alpha-methopterin and aminopterin. Great improvement has followed the administration of these substances in certain cases of leukaemia and Hodgkin's disease, but the results appear to be of a transitory nature. Whatever their ultimate position in cancer therapy will be, they are of very great theoretical importance.

Professor Dodds also drew attention to the point made recently by Sir Robert Robinson—namely, that a number of amino-acids can be regarded as building-stones not only for proteins but also for alkaloids. Thus ornithine may be regarded as one of the originating substances of some coca bases.

Protein Composition

Dr. Kenneth Bailey described some features of the amino-acid composition of proteins and pointed out that exact amino-acid analyses, such as Sanger's work on insulin, were of great use in determining the make-up of proteins but did not disclose much about their physico-chemical nature. In nutrition research determination of the amino-acid make-up of the mixed proteins of the individual foodstuffs was of value. Dr. Bailey reported that when he plotted reliable data, such as Tristram's on amino-acid composition, in the form of a histogram he found that the essential amino-acids fell within a much narrower frequency range than did the dispensable amino-acids. This would indicate that with the exception of incomplete proteins such as zein and gelatin most proteins have relatively constant proportions of those amino-acids which are found to be essential in the diet. Dr. Synge also emphasized the uniformity of the mixtures of amino-acids encountered in nature. He thought this should lead in the near future to a systematization of procedures for determining amino-acids, though much further work was necessary on the more complicated substances such as peptides. Dr. Neuberger referred to the changed outlook on the chemistry of the proteins which had taken place between the two world wars, and Dr. Tristram and Dr. Barton-Wright described the chemical and microbiological methods for the determination of the amino-acid composition of proteins.

Dr. Lea drew attention to the amino-acid or Browning reaction which occurs in aqueous solution, or in the comparatively "dry" state, between protein or amino-acids and sugars to produce changes in odour, flavour, colour, solubility, etc. The net effect of this is sometimes desirable and purposely sought, but in other instances is highly undesirable, even sometimes amounting to a loss in the biological value of the protein. Investigations with dried milk and other foodstuffs have shown that the most rapid of the chemical reactions is a combination of the reducing sugar with the free amino groups of the protein. Since these are very largely the ε-amino groups of the lysine side-chains a nutritional deficiency of this amino-acid may result. The use of hydrolysed protein and of amino-acids as flavouring agents was considered by Dr. Rees: in small amount (0.05–0.5%) the monosodium salt of glutamic acid is said to improve and enhance the flavour of the food.

Dr. Dyson and Mr. Bavin described the careful methods which are necessary for the preparation of an enzymic hydrolysate of casein so that it is sterile, pyrogen- and anaphylactogen-free, and does not cause blood-pressure changes on administration. Precautions are also taken to reduce the deposition of tyrosine. These speakers also drew attention to the work of Geyer and his colleagues[21] on the usefulness of a fat emulsion in which the particle size is not more than two microns. This emulsion can be autoclaved and administered in 30% concentration without the risk of embolism.

Protein Metabolism

Dr. D. P. Cuthbertson reviewed the comparative physiology and pathology of amino-acid and protein metabolism and drew particular attention to Rose's[22] latest account of his human experiments on amino-acids and hydrolysates of protein for the maintenance of nitrogen equilibrium in man. The latter had found that for maintenance the eight amino-acids, *l*-tryptophan (0.25 g.), *l*-phenylalanine (1.10 g.), *l*-methionine (1.10 g.), *l*-leucine (1.10 g.), *l*-isoleucine (0.70 g.), *l*-valine (0.80 g.), *l*-threonine (0.50 g.), and *l*-lysine (0.80 g.), are necessary (his assessment of the minimum daily requirements of each for the adult is indicated in parentheses, but he recommends as the daily intake twice these amounts.) For the growing human organism histidine and arginine are probably necessary, and it may be that some of the amino-acids thought at present to be dispensable may be necessary if the synthetic capacity is liable to be overtaxed, for the human requirements of amino-acids for pregnancy and lactation or in different forms of illness are still not known. Rose has found disconcerting differences in the minimum amount of amino-acid required by different individuals under comparable experimental conditions. With certain amino-acids the results are consistent, with others there may be as much as a 100% difference. While the role of methionine, cystine, and vitamin E in the prevention of experimental acute liver necrosis is still not very clear, progress is being made. The recent observation by Patt and his colleagues[23] on the protective action of cysteine on rats exposed to *x*-radiation is also of considerable interest.

Dr. Cuthbertson stressed the relative constancy of the intake of protein in dietary surveys of all classes and at all energy levels in temperate climates when the protein is expressed as a percentage of total calories. This occurs at all ages from one year onwards. All the normal physiological states appear to be covered when the protein intake lies between 11 and 14% of the calories, the higher values being related to growth, reproduction, and lactation. The speaker also discussed protein insufficiency, the effects of trauma and infection, and the requirements for convalescence, as outlined in a recent paper by him in this *Journal*.[24]

JUVENILE DELINQUENCY

FIELDS FOR FUTURE RESEARCH

A conference on the scientific study of juvenile delinquency was held on October 1 at the Royal Institution, London. It was convened by the National Association for Mental Health, the Royal Medico-Psychological Association, and other bodies, and was opened by the Earl of Feversham, president of the National Association of Probation Officers. Introductory remarks were made by Miss Cecily Craven and by Mr. Alec Rodger, honorary secretaries respectively of the Howard League for Penal Reform and the British Psychological Society. The conference was attended by representatives of Government departments, local authorities, the magistracy, the Church, educational bodies, and voluntary and youth organizations. The Home Secretary, in a message, said that the Home Office was considering the question of Government assistance for research.

Limits of Present Knowledge

Dr. J. D. W. Pearce, medical co-director, Portman Clinic (Institute for the Scientific Treatment of Delinquency), said that much of the work on this subject had been handicapped by lack of knowledge of scientific method and by rather woolly recording. A difficulty had been the absence of adequate control groups, but a great deal was known about the intelligence and educational attainment of the juvenile delinquent. Many delinquents were skilful and therefore were never caught, so that it might be that the intelligence of delinquents in general was ranked too low and more nearly approximated to average intelligence. Something was known also of the problems of psychopathic personality and temperamental instability, though there was still disagreement about how far the latter was constitutional or acquired. Electroencephalographic studies were helping to throw light on conduct disorders. Sir David Henderson had reported cases in which cerebral surgery in adult criminals had brought about a remarkable change in character; but these things were in their infancy. Something was known about the psychological mechanism involved in delinquency, not only in the individual but in the group. Clinical types could be identified and treatment prescribed; prescription might be relatively easy and administration more difficult. Individual psychotherapy based on sound analytical

training had revealed a great deal about aetiology. Facilities for observation, care, treatment, selection, grouping, and experiment, however, were inadequate. Rarely was delinquent conduct to be explained by a simple cause; nearly always there were many factors concerned.

Dr. H. MANNHEIM, reader in criminology, London School of Economics, agreed that in this matter of the young delinquent all too often half-baked truths and slogans took the place of exact scientific knowledge. The weakness of most investigations —Sir Cyril Burt's *The Young Delinquent*, first published in 1925, was an exception—was that they were exclusively based on court cases; consequently very little was known about delinquents who did not appear in court or about non-delinquents who in essential characteristics resembled delinquents. Non-court cases ought to be included in any study. Dr. Mannheim, at the end of his paper, asked whether the research done so far had been of any practical use to anybody —to the legislator and administrator or to the practical worker in the field. Sixteen years ago Sir Alexander Paterson wrote a paper entitled, "Should the Criminologist be Encouraged?" He was not sure of the answer, apparently, but the greatest encouragement the criminologist could desire would be a favourable answer to the question he had put.

Personality and Social Factors

Dr. JOHN BOWLBY, director, Child Guidance Department, Tavistock Clinic, mentioned three false assumptions by which research in the past had been vitiated: (1) that delinquency was clear-cut and distinct from other forms of behaviour; (2) that there was no necessity for qualitative distinctions; and (3) that the problem could be studied by concentrating on cases brought into court. Little light would have been cast on the problem of malnutrition if physiologists and physicians had not studied large samples of the population irrespective of whether they came into hospital or not; many most informative studies on nutrition had been made outside the clinic. It was only a specially selected group of delinquents who came into court. Public-school boys rarely came before juvenile courts. Was that because they never stole or because their parents and schoolmasters dealt with them in some other way?

Individual susceptibility to adverse influences was clearly a psychological problem. Why was it that some individuals grew up more susceptible to antisocial influences than others? Research in child development suggested that it depended on the relation which the child had with his parents in his early years. Two factors specially common in the history of persistent delinquents were prolonged separation (not less than six months) of the child from his mother during the first five years, and the child being unwanted by parents who were themselves unstable and unhappy. Blanket generalizations regarding "family atmosphere" and "broken homes" were as useless as would be similar generalizations about diet in research on nutrition. A thorough analysis of the young child's social "diet" was required for a study of antisocial attitudes.

Dr. Bowlby suggested that a worth-while project in this field of research would require from 12 to 20 professional workers, a corresponding number of clerks and secretaries, a period of five or eight years, and an expenditure of £15,000 to £20,000 a year. The sum spent on research on nutrition, which had paid such splendid dividends, far outstripped these totals. "The whole of medical and sociological research could be financed for a decade out of the sums spent on the development of the Brabazon."

Professor T. S. SIMEY, Department of Social Science, University of Liverpool, said that it was not justifiable to consider the characteristics, behaviour, and treatment of the delinquent as an isolated individual. Not even the adult criminal, still less the young offender, should be considered as something essentially "different" merely because he had been found guilty of breaking the law. Crime was the result of dysfunction within the society in which it took place.

Call for a Central Research Body

A central authority to initiate, execute, and co-ordinate research and to provide technical advice was called for by Professor Simey, and the same idea was taken up by the last contributor to the symposium, Dr. DENNIS CARROLL, medical co-director of the Portman Clinic, who said that there was a case for setting up a "Delinquency Research Council," possibly covering social research in general. There was no shortage of suitable experienced individual advisers, but for the many highly expensive and complicated researches required such a central authoritative body would have the advantage of commanding enough money and enough general support to make the practical task really effective. For example, there was need for a thorough survey of probation to discover the best criteria for placing an offender on probation and the best form of probationary care. Many other things could be discovered at the same time, and some of them would quite likely lead to the development of special educational systems for certain ascertainable types of offender, such as the potential recidivist, the young psychopath, or the unstable dullard.

Dr. Carroll mentioned some generally unchallenged statements, such as that parental control had diminished, that religious faith had declined, that boys' clubs were a major weapon in preventing delinquency—all of which were plausible and probable, but none of them supported by studies which could withstand scientific criticism. Much was heard about defective control of children, but it was not always the fault of the parents; on the religious question it was very hard to avoid subjective bias; and as for boys' clubs, a survey in 1942, *Young Offenders*, by Carr Saunders and others, gave information which cast some doubt on the general assumption, though it did not settle the issue. It was not that these assumptions were necessarily wrong, but they were accepted without proof. Incidentally Dr. Carroll suggested that the Press might try to design a system of crime reporting which would have crime prevention as its main object. Finally he laid stress on the importance of keeping such records and statistics as would make it possible for others dealing with delinquents to know exactly what had happened.

MEDICAL PROTECTION SOCIETY

ANNUAL MEETING

The annual meeting of the Medical Protection Society (formerly the "London and Counties") was held at Victory House, Leicester Square, on September 28. Sir Ernest Rock Carling, who presided, referred with regret to the loss during the year of three vice-presidents—Dr. G. M. Stoker, Sir Edmund Spriggs, and Professor Harry Stobie. He welcomed as new members of Council Mr. H. L. Hardwick and Dr. J. H. Hunt.

The relation of the Society to the other two defence societies, Sir Ernest Rock Carling continued, was fruitful in many directions. On the question of sterilization the three societies had jointly sought the opinion of counsel, which was that the only circumstances in which a sterilizing operation could be rightfully performed were those in which the operator honestly believed upon reasonable grounds that such an operation was necessary to preserve the life of the patient or to avoid serious injury to his physical or mental health. A doctor should make sure that such danger existed, should obtain where possible a second opinion, should make plain to the patient the results of the operation, and obtain his consent in writing, freely given without undue influence by others. In such circumstances both surgeon and patient would be safe from any suggestion of illegality.

The Society did a great deal more for its members than appeared in the pages of its report. In addition to the cases which came before the Legal Committee, something like 40 applications a week were received for assistance, many of them in matters which, strictly speaking, were not within the Society's scope. The Society had been glad on several occasions to help —although it could not represent—members at hearings before medical or dental service committees under the National Health Service, as well as to appear for members at appeals. It was extremely important that the Society should receive the earliest possible information of any charge brought against a member.

A circular was issued by the Home Office forbidding the payment to salaried officers in the National Health Service of allowances as professional witnesses for attendance at court. The Society had taken the opinion of counsel, who advised that certain paragraphs of the Home Office circular were conflicting and had no legal force. A suitable case coming before an assize court, counsel was instructed to raise the matter of fees, and the judge ruled that the direction in the Home Office circular was too narrow. An intimation had now been received from the Home Office that the part of the circular which laid down these restrictions had been withdrawn.

An influential member had written to the Society to suggest that its insistence upon *x*-ray evidence in all cases of injury and the like was inexpedient in view of the cost and present shortage of *x*-ray films, but Sir Ernest Rock Carling, while mindful of economy, thought it would be a very unfortunate thing if such evidence were not obtained. It was the legal profession rather than the medical which required education in this matter. Other precautions which the experience of cases had emphasized during the year were the necessity for extreme care in the administration of intravenous fluids and the perennial matter of the checking of swabs. He was inclined to think that some authoritative body ought to undertake a survey of the methods of checking swabs, their recording and recovery. The Society had taken up the question of hypodermic needles broken in the course of an injection, and he thought that on every occasion the metallurgist had reported an actual defect in the needle.

Sir Ernest Rock Carling was unanimously re-elected, as were the retiring vice-presidents and other officers. The annual report, which was adopted, embodied a statement by the solicitors (Messrs. Le Brasseur and Oakley), who wrote:

"... should it have been in the mind of any member that the advent of this [National Health] Service would render the protection of your Society unnecessary, the experience of the first year of the Service has most emphatically proved the contrary. . . . New risks have been created and new problems have arisen calling for advice. Our experience and that of the Society has been that more applications have been received from members for advice and guidance than at any previous time in the life of the Society. A new bureaucracy has been created, and though the various committees and tribunals are all under the Minister of Health the Minister has shown in our present experience a decided disinclination to interfere with the dicta of such bodies excepting in cases where there is a right of appeal."

Arab refugee children from Palestine in the Middle East area are being vaccinated against tuberculosis by Scandinavian medical teams, under the sponsorship of UNICEF, the United Nations International Children's Emergency Fund. Some 250,000 refugee children under 18 in Lebanon, Syria, Transjordan, and Palestine are being tuberculin-tested, and all who require it will be vaccinated to protect them against the disease. Tuberculosis has been a cause of increasing concern to medical officers in the refugee areas. There are hundreds of thousands of refugees in North and South Palestine and surrounding countries, living in tent camps, overcrowded and devastated villages, many in caves, shanties, and other improvised means of shelter. Five special vaccination teams, consisting of one doctor and four nurses each, were recruited in Denmark, Norway, and Sweden. These are skilled vaccinators, most of whom worked for some time in the joint UNICEF–Scandinavian International Tuberculosis Campaign in various countries of Europe. It is expected that they will complete the vaccinations of the refugees in about three months. Vehicles and medical supplies for the refugee vaccination programme were provided by UNICEF. The vaccine is being delivered regularly by air from the Danish State Serum Institute in Copenhagen to Beirut, Lebanon, for subsequent distribution to the vaccination centres. The vaccination programme is conducted in close co-operation with the medical officers of UNRPR (United Nations Relief for Palestine Refugees) and of the three agencies which are caring for the refugees: the League of Red Cross Societies, the International Committee of the Red Cross, and the American Friends Service Committee (Quakers). Dr. Mogens Fog-Poulsen, of Aarhus, Denmark, is chief of the mission.

NEW HUNTER DOCUMENTS EXHIBITED

The Hunterian Society held a cocktail party, instead of its annual dinner, on October 6, and displayed an interesting collection of historical relics which are in the curatorship of Mr. C. Robert Rudolf. Chief among them were legal documents relating to John Hunter and his eldest son, John Banks Hunter, which recently came to light and were displayed for the first time. John Banks Hunter was born eleven months after John Hunter's marriage and received his second name after his father's friend, Joseph Banks, the naturalist. His life is something of a mystery. He entered St. John's, Cambridge, but left without a degree and joined the Army. After serving for a number of years he bought himself out and went to live at Toulouse. There appears to have been some trouble, for Mrs. Hunter wrote in 1810 of "my poor unhappy son," and another relative refers to the eccentric cousin.

The new documents shown at the Hunterian Society concerned the earlier wills of this son, the first being the original sealed will of "John Banks Hunter (John Hunter Junior) Ensign in the 2nd Battalion Royal Regiment of Foot, dated July 18, 1794." The testator left his property to his mother, or, if she was deceased, to his only sister Agnes. There was a note in the will: "Add the freedom to Geo. Bristow"—a slave kept by Hunter, the provision for whose release is referred to in the next will, dated December 12, 1804. The second will is very similar to the first; it is interesting that J. B. Hunter should have used the crest of his father (then dead eleven years) to seal it. Later, twelve years after his mother's death, J. B. Hunter made another will, of which a photostat copy was shown, leaving his property in Scotland to his sister, but his personal estate to a friend in Toulouse. The absence of any reference to a wife seems to confirm what is stated in the *Reminiscences* of Elizabeth, daughter of Matthew Baillie, written 1866–8 (Royal College of Surgeons MSS), that J. B. Hunter died unmarried.

The new documents relating to the estate of John Hunter himself were a lawyer's copy of his will, and two drafts of a power of attorney by the son and heir on his going to Corsica. Among other recent acquisitions were snuff boxes belonging to John Hunter and also to a Dr. John Hunter who practised in the Minories and is stated to have been a friend of his illustrious namesake. There were also shown an original Laennec stethoscope, whose proportions were exactly those of the instrument illustrated in its inventor's *Traité de l'Auscultation Médiate* (Paris, 1818), and a tinted silhouette of Jenner.

The rest of the exhibition was devoted to the history of the Society, including a letter from Mr. T. J. Armiger, assistant surgeon to the London Hospital, who suggested the Society's foundation, and a reply in verse by the present Poet Laureate to an invitation from the Society. The Society's custom of holding an annual dinner was instituted during the presidency of Dr. Benjamin Robinson; a manuscript of his on a case of intestinal disease was also exhibited.

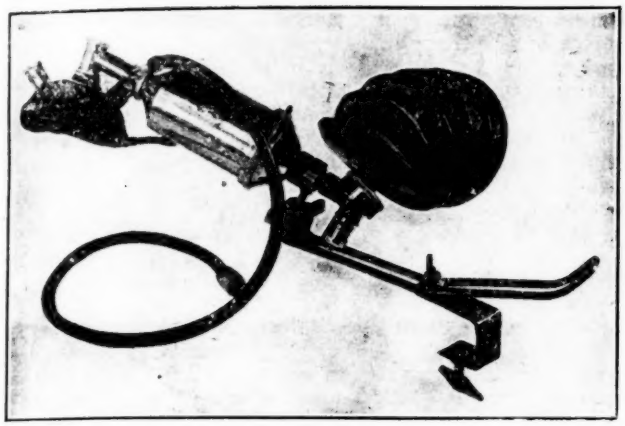
Preparations and Appliances

A MODIFIED WATERS APPARATUS FOR THORACIC SURGERY

Dr. W. B. Bacon, visiting anaesthetist to the Royal Manchester Children's Hospital, St. Mary's Hospital, and Christie Hospital, writes: One of the difficulties with a Waters canister is the secure anchorage of the heavy soda-lime container. This is overcome by a simple clamp, fitting any operating table, to which a slotted length of steel about 14 in. (35 cm.) long is secured by means of a wing nut. This steel arm at its distal end carries a ball-and-socket joint which holds the canister and bag. The arm slides on the table clamp to any desired position, and the ball joint can be locked in any position suitable for holding the canister. Instead of the usual rubber bag the

Oxford vaporizer concertina type of bag is used, the capacity of which is 2.84 litres. There is an inspiratory valve and pressure gauge mounted on the bag fitting.

In addition to the usual expiratory valve on the Waters mounting an expiratory valve is fitted on the facepiece as near the rubber rim as possible, thus reducing as much as possible the dead space. Between the canister mount and the canister is an easily removable copper-gauze filter of the finest mesh. This is inserted in order to reduce the blow-over of soda-lime powder. It has not been found to increase breathing resistance to any appreciable extent. It is easy to remove the canister, readjust the holding mechanism, and use the apparatus for assisted breathing should this be required, as often happens during the



administration of curare. The photograph shows the apparatus with the soda-lime canister.

Leigh and Belton, in their recent book on paediatric anaesthesia, state that the soda-lime in the end of the canister nearest the facepiece is used up first, thus creating an additional dead space. They advise the use of a reversible canister. I use this apparatus at the Royal Manchester Children's Hospital for such procedures as Blalock's and Pott's operations for pulmonary stenosis. In these cases it is essential to have perfect control over respiration; the concertina type of bag, mounted near the child's head, materially helps this control. Cyclopropane is given, and it is my practice to use a Cobb's connector with the largest endotracheal tube (consistent with safety for the larynx), thus giving easy access for catheter aspiration. A facepiece, with gamgee pad, is employed instead of an endotracheal mount, as it is found that a better gas-tight joint is obtained, giving more efficient control of respiration, particularly when positive pressure is required for inflation of the lung.

All chest cases leave the theatre with the apparatus (without canister) attached; expiratory valves are fully open and a flow of not less than 6 litres per minute of oxygen is supplied from a cylinder attached to the bed. Not until the patient is safely transferred to the ward, and breathing is satisfactory, is the apparatus detached. Adults continue oxygen inhalation either by B.L.B. mask or by spectacle, according to their condition; children are housed in an oxygen tent.

I am indebted to Mr. Wardlaw, of the Christie Hospital, for the photograph, and to the British Oxygen Company for making the apparatus.

The British Rheumatic Association at its annual general meeting elected Colonel Stoddart-Scott, M.P., chairman. Air Vice-Marshal Don and Dr. Francis Bach were elected vice-chairmen for the coming year. Among the nearly one million disabled persons registered, only 35,000 are rheumatic sufferers, and these are mostly ex-Servicemen. The British Rheumatic Association is concerned to secure the privileges available under the Act for the large number of rheumatic sufferers who could benefit by it.

Correspondence

Tuberculosis: Certain Unexplained Mortality Figures

SIR,—Mr. G. Herdan (September 24, p. 706) has conveyed the impression, which is erroneous, that the ageing of the Scottish population is sufficient to explain most of the changes in the mortality from pulmonary tuberculosis in that country to which Mr. Walter Elliot (August 6, p. 297) had drawn attention.

In support of his contention Mr. Herdan has adduced a very roundabout argument, but, most strangely, he has failed to make a full examination of the available direct evidence—the mortality in specific age groups for each sex separately. These mortality rates are unaffected by changes in the age distribution of the population. I present them below; they show quite clearly that the changes in the mortality from pulmonary tuberculosis in Scotland, and in particular the divergence from the experience in England and Wales, cannot be dismissed as a statistical fiction.

TABLE I.—*Annual Civilian Deaths from Tuberculosis of the Respiratory System per 100,000 Civilian Population by Age and Sex in England and Wales and in Scotland, 1939 to 1947*

	Age Group				
	15–24	25–34	35–44	45–54	55–64
Males:					
England and Wales					
1939–41	67	93	97	120	124
1942–44	78	127	98	115	121
1945–47	56	80	75	104	118
Scotland					
1939–41	80	105	105	115	91
1942–44	97	127	105	109	98
1945–47	82	104	100	113	110
Females:					
England and Wales					
1939–41	85	75	49	35	31
1942–44	80	69	41	30	27
1945–47	72	69	40	27	24
Scotland					
1939–41	116	92	51	35	29
1942–44	143	99	52	28	27
1945–47	135	132	51	28	22

Table I presents the civilian mortality from the disease in England and Wales and in Scotland. To save space the death rates are given for triennial periods, but the annual figures also justify the comments which follow. Figures for Scotland in 1947 were kindly supplied to me by the General Registry Office in Edinburgh. Otherwise the information is taken from the published reports of the Registrars-General.

Males.—In England and Wales the mortality of civilian males aged 15–34 increased during the war and then dropped substantially in the period 1945–7. In the older age groups the death rate was fairly constant during the war period, and afterwards declined. The picture in Scotland for young adults was similar to that in England, but at older ages the rates increased slightly after the end of the war.

Females.—For civilian females in England and Wales the mortality in each age group declined during the period studied. In Scotland there was between 1939–41 and 1942–4 a definite increase in the death rate amongst those aged 15–34, the rates for the older women remaining steady. By 1945–7 the mortality had increased still further for the women aged 25–34; for the other age groups it remained at the 1942–4 level.

The civilian mortality rates from pulmonary tuberculosis were presumably inflated in both countries during the war years by selective recruitment of the more healthy individuals for military service. It may be assumed that the effect upon the death rates was very similar in the two countries, since the same conscription laws applied to both. Hence the ratio of the tuberculosis death rates in the two countries will be largely unaffected by selective recruitment. This comparison is presented in Table II, and it indicates the extent to which the Scottish experience has diverged both during and since the war from that in England.

TABLE II.—*Ratio of Civilian Mortality from Tuberculosis of the Respiratory System in Scotland to that in England and Wales, by Age and Sex, 1939 to 1947*

	Age Group				
	15–24	25–34	35–44	45–54	55–64
Males:					
1939–41	1·19	1·13	1·08	0·96	0·73
1942–44	1·24	1·00	1·07	0·95	0·81
1945–47	1·46	1·30	1·33	1·09	0·93
Females:					
1939–41	1·36	1·23	1·04	1·00	0·94
1942–44	1·79	1·43	1·27	0·93	1·00
1945–47	1·88	1·91	1·28	1·04	0·92

An example will make the interpretation of this table clear. The ratio of 1.19 for males aged 15–24 years in 1939–41 means that the pulmonary tuberculosis mortality among males of this age group was 19% above that in England. In 1942–4 the excess was 24%, and in 1945–7 it amounted to 46%. The other age groups indicate a similar (though lesser) deterioration of the Scottish experience in 1945–7 relative to that in England. Among females the divergence between the Scottish and English rates is particularly noticeable for those women aged 15–34. During the period 1945–7 the rates in Scotland were about 90% greater than those in England.

The statistical evidence thus indicates that: (1) the mortality from pulmonary tuberculosis among young adults in Scotland compares very unfavourably with that in England and Wales, and is relatively much worse now than it was early in the war; (2) the increase which has occurred since the war in the death rate from the disease amongst Scottish women aged 15–34 is a matter meriting the fullest investigation.—I am, etc.,

Oxford. IAN SUTHERLAND.

Modern Trends in Radiology

SIR,—The rather curious views propounded by Dr. James F. Brailsford (October 1, p. 724) as representing modern trends in radiology are not likely to be supported by his clinical and radiological colleagues. It is notable that in the bibliography all the references are to himself. He has always been an opponent of case finding as a method of control of tuberculosis, and states that "it can be proved to have been responsible for the infliction of much mental and physical pain." The following are the facts.

In this country three and a half million people volunteered for mass radiography. As a result of the initial examination 13,401 were found to be suffering from active tuberculosis necessitating treatment. Samples of these patients compared with samples of patients reporting with symptoms to chest clinics have shown that those detected by mass radiography require from six to seven months' treatment before returning to work, as against eighteen months to two years required by those reporting to chest clinics.

A still larger group of individuals with minimal tuberculous lesions or lesions of doubtful activity detected by mass radiography have been kept under observation while at work. Presumably it is in this group that Dr. Brailsford believes that we are inflicting physical and mental pain. Chest physicians following up these cases and contact cases do not report any adverse mental or physical effects on the individuals concerned. If Dr. Brailsford has facts and figures supporting his contention that these simple procedures are being so badly handled as to cause serious neuroses it is high time he produced them.

Dr. Brailsford, in similar vein, makes a surprising criticism of Professor Morgan's work on the early diagnosis of carcinoma of the stomach, and suggests that he abandons it until "a cure for malignant disease is discovered." It is not misinterpreting Dr. Brailsford to summarize his views on the diagnosis of tuberculosis and carcinoma as follows—wait until the patient has a big haemoptysis or a palpable tumour.

Time prevents me from commenting on many other statements in this article which cannot be substantiated by facts. Its general tenor can be judged by such remarks as, "Mass surveys are essentially bureaucratic regimental measures, designed by officials and enthusiasts." And again, injection of opaque media "can, in the long run, result in atrocities, cruelties, or licensed murder." It is deplorable that such nonsense should have been given space in a scientific journal.—I am, etc.,

London, W.1. PETER KERLEY.

SIR,—Dr. J. F. Brailsford (October 1, p. 724) is again severely critical on the subject of mass radiography. Let us analyse some of his objections for what they are worth.

First he says, "Mass surveys are essentially bureaucratic regimentation." As far as chest radiography is concerned nothing could be further from the truth. The whole procedure is entirely voluntary from the first miniature film taken to the final clinical examination in abnormal cases. The fact that a number of people are able to pass through the unit in a short space of time smacks no more of bureaucracy than does the walking through the turnstiles of the Motor Show.

Secondly he says, "Mass radiography has added nothing new to our knowledge of radiography of the chest." Here again I would dispute his words very strongly. Quite apart from pulmonary tuberculosis, what about the unsuspected early neoplasms which are discovered? Up to the end of 1947 257 cases of pulmonary neoplasm were picked up by units in this country, 198 of which are known to have been referred to thoracic surgical units (Ministry of Health figures).

Apart from Dr. Brailsford, I think that practically every physician in the country recognizes and applauds the early detection of pulmonary tuberculosis by miniature radiography or any other means. Every experienced worker in the field of tuberculosis knows that some lesions, even if they appear soft radiologically, do not progress over a period of years, whereas others will spread rapidly. What nobody can yet say is exactly which type of lesion will or will not heal. Our knowledge in this field can only be broadened by the serial observation of more and more of these unsuspected cases.

The "stigma of being labelled tuberculous," which Dr. Brailsford so greatly fears, is surely diminishing in this enlightened age and will continue to do so if we find and boldly follow up all types of case.—I am, etc.,

Keresley, near Coventry. A. GORDON EVANS.

SIR,—No one could doubt the truth of Dr. James F. Brailsford's statement (October 1, p. 724) that there would be fewer errors in the interpretation of radiographs if radiology was always preceded by a sound clinical examination, but the second part of his statement, as far as diseases of the chest are concerned, is simply untrue and quite unsupported by experience.

I do not know how many chests Dr. Brailsford examines clinically, but I can put my experience on record. Of the 31 cases of pulmonary tuberculosis now awaiting admission for sanatorium treatment from my area, only 10 patients had signs which were revealed by clinical examination by, at least, two different examiners. One of the 10 patients has a large pleural effusion, five have far advanced, extensive, and incurable lesions, and only four have some chance of recovery by adequate treatment. Had, in the other 21 cases, radiography been omitted in favour of a negative clinical examination the consequences would have been disastrous.

It is highly regrettable that at the time when in medical papers all responsible workers who know every aspect of tuberculosis incessantly try to impress on the general practitioners the absolute necessity of referring all suspicious cases for a radiological examination as early as possible, notwithstanding whether clinical examination reveals any signs, unqualified views should be expressed with apparent authority to the effect that "the least harm will come from omission of the radiograph and most from omission of the clinical examination." Such a statement, without any evidence to support it and quite contrary to the experience of all chest physicians, can only achieve one purpose, to confuse the general practitioners, who to a great extent rely on the reading of scientific papers, and to diminish the co-operation with chest physicians with the result of losing valuable time and lives.

As regards Dr. Brailsford's remarks on mass radiography, is it possible that Dr. Brailsford has in the heat of the argument momentarily forgotten that tuberculosis is an infectious disease? I recently experienced some difficulty in persuading a young bus driver who "never lost a day's work" to be examined at the clinic after his 14-months-old baby had died of miliary tuberculosis. Actually his views, probably obtained from the lay press, were very much like those expressed by Dr. Brailsford, but at last he gave in and his *x*-ray film showed a large cavity in the left apex and his sputum was positive. Does Dr. Brailsford really think that in this case, and in similar cases which are a commonplace experience in any chest clinic, that a mass radiography survey, which would have picked up this man before fatally infecting his child, would have only "seriously interfered with his life without contributing any good"?

Every sane person will agree with Dr. Brailsford that "there would appear to be no more justification for removing a healed or quiescent lesion of the lung (which would not have been suspected if there had been no radiograph) than of any other structure, or in fact for removing any normal tissue; since valuable healthy lung is removed." But this sentence, read together with the previous paragraph stating that "the most successful surgical results have been obtained in cases which have previously healed themselves and are symptomless," implies that thoracic surgeons quite unnecessarily perform mutilating operations on patients with healed lesions. I doubt very much whether Dr. Brailsford really realizes the seriousness of this charge. A surgeon who would perform a major and often mutilating operation unnecessarily would be guilty not only of gross ignorance but at the same time he would expose himself technically to a legal suit by the patient for causing grievous bodily harm. It is not certain to me whether Dr. Brailsford levelled this very serious charge against American surgeons based upon his American experiences or whether he left in his American audience the impression that this sort of thing is being done by British thoracic surgeons, but the fact is that the reputation of British medicine and surgery is still very high in the United States and such a serious accusation should not pass unchallenged. As these utterances were made not only in print but apparently in several lectures in the United States, Dr. Brailsford should either substantiate this statement by incontrovertible evidence or should withdraw it publicly without reservation.—I am, etc.,

Colchester, Essex. F. KELLERMAN.

Essential Hypertension in Pregnancy

SIR,—I feel it my duty publicly to acknowledge how deeply I deplore the fact that I have misunderstood Mr. R. H. Paramore's ideas on the mechanism which induces hypertension and causes renal cortical ischaemia in pregnancy. I might possibly be excused on account of the way in which Mr. Paramore expressed his ideas in his letter in the *Journal* of August 27 (p. 486). I quote from this letter: "In my view spinal analgesia acts by inducing a state comparable with shock. There is a great fall of blood pressure, and blood is not thrust into the renal medulla to maintain the obstruction to the exit of urine from the uriniferous tubules." To me it seems logical that if the belief of Mr. Paramore was that the spinal analgesia helped by preventing the blood from being thrust into the renal medulla it was because he thought this to be the responsible factor. However, as no one could know Mr. Paramore's ideas on the subject better than himself I am really admitting my mistake and again plead to be pardoned for my apparent lack of clairvoyance.

One thing I can state without hesitation—namely, that my letter (September 17, p. 650) answering Mr. Paramore's direct reference to me and to the book in the writing of which I collaborated was not dictated under any "misapprehension"; on the contrary, it was written with all sympathy to Mr. Paramore for his pioneer contribution to the treatment of eclamptic patients by means of spinal analgesia.—I am, etc.,

Oxford. J. TRUETA.

*** This correspondence is now closed.—ED., *B.M.J.*

A New Neonatal Syndrome

SIR,—In reference to the letter by Drs. Crystal Bates and A. P. M. Page (October 1, p. 756) adding another case to the interesting series published by Mr. W. G. Mills (August 27, p. 464), we should like to record that we have seen 20 similar cases in Liverpool, the details of which we intend to publish shortly. We believe these cases were due to the intra-arterial injection of "cycliton," but we have not seen similar effects follow the use of lobeline.—We are, etc.,

F. P. HUDSON.
Liverpool. ANNE MCCANDLESS.

Penicillin in Early Syphilis

SIR,—Your annotation on this subject (September 24, p. 694) presented in able fashion the position at this moment of transition, but I should like to take exception to the statement that the results of Eames and Miller (p. 672) "are appreciably worse than those reported *after similar treatment* [my italics] by McElligott, Jefferiss, and Willcox." Surely, Sir, the secret of the better results obtained by the latter method[1] lies in the choice of a more effective arsenic and bismuth course rather than in the method of employing penicillin, since it is generally accepted that the method using a daily single shot of penicillin in oil-beeswax is not superior to the three-hourly regime of adequate penicillin dosage in aqueous solution. The essential basis of this course consists in the concurrent administration of arsenic and bismuth twice weekly over a period of six weeks,[2 3] and the Ministry of Health recognized its value in preventing clinical and serological relapse in 1943.[4]—I am, etc.,

Liverpool. O. A. F. ROSS.

REFERENCES

1 *Brit. J. vener. Dis.*, 1948, **24**, 45.
2 Ross, A. O. F., *Lancet*, 1930, **2**, 1206.
3 —— *Brit. J. vener. Dis.*, 1945, **21**, 123.
4 Ministry of Health Recommendations on the Treatment of Merchant Seamen, ibid., 1943, **19**, 77.

Myxoedematous Madness

SIR,—Dr. R. Asher's article on myxoedematous madness (September 10, p. 555) gave prominence to hypothyroidism as the aetiological factor in certain psychoses. The exhibition of thyroid extract in psychoses has frequently been tried with disappointing results, except in some cases of schizophrenia, and apart from myxoedema the mechanism of the therapy is very obscure. Hyperthyroidism is classified as a psychosomatic illness, and a considerable proportion of cases are an expression of an anxiety state. Occasionally it is associated with a manic-depressive psychosis. Because of this rare association of thyroid dyscrasia and psychosis I feel the following case is worthy of quotation.

A married woman, aged 49, came to see me in March, 1948. She was depressed and sleepless at nights. She felt "awful" in the mornings and found everything too much trouble. There was no evidence of physical disease, and I decided she was a case of mild involutional depression. She responded well to dextro-amphetamine sulphate and a sedative at night; but when after a year of this treatment she was much the same and very dependent on drugs I decided it was time she saw a psychiatrist. He agreed with my diagnosis and advised E.C.T., but she could not face the idea of a mental hospital.

In April, 1949, she became profoundly depressed. She felt so wretched she said she would agree to any treatment and went as a voluntary patient to a mental hospital. She stayed there for five days and then returned home as bad as ever. I was loath to certify her, and while I was observing her the picture changed completely and dramatically: within a month she was the picture of thyrotoxicosis. She lost weight, sweated profusely, had a tachycardia, and her thyroid gland enlarged. She looked a textbook picture. With the advent of this new syndrome her depression vanished. She became cheerful and started eating and sleeping. Thyrotoxicosis was confirmed at the local hospital, and she was put on the waiting-list for operation. Her admission was delayed until July, 1949, during which time she became manic. She arose at 4 a.m. and cleaned her house from top to bottom. She could not keep still—this with a pulse of 140 and oedema of her ankles. These symptoms subsided

on thiouracil, and when she was finally admitted for operation there was no marked psychic abnormality. Her thyroidectomy was uneventful, and she is now her normal self. She is still a bit apprehensive about exerting herself and doing a full day's work, but she eats well and sleeps well and keeps cheerful without any marked swing of affect.

In this case thyroid auto-intoxication appeared to raise endogenous depression. Mania intervened but was controlled by thiouracil. Thyroidectomy appears to have cleared the condition except for some residual anxiety such as one would expect after such a long illness. Was this a series of coincidences, or was there cause and effect? As in Dr. Asher's cases thyroid alleviated the condition, but she was no case of myxoedema in the first instance.—I am, etc.,

Ibstock, Leics. C. A. H. Watts.

Sir,—I feel confident that Dr. E. B. Davies has indeed earned the gratitude of all physicians and psychiatrists with his interesting letter (September 24, p. 706) on myxoedematous madness. When we next encounter a case of myxoedema with psychosis we must earnestly remind ourselves that the association of these two relatively rare disorders is probably fortuitous. Moreover, should the mental symptoms disappear as the myxoedema responds to thyroid we must remember that this, also, is likely to be accidental. After all, psychoses do remit or subside spontaneously.

On the other hand, if we have helped a psychotic patient to recall with emotion some highly significant event, such as, for example, having seen in childhood his mother or her father in the bath, we may rejoice at having struck gold. For then we can be quite certain that we have skilfully unearthed the specific cause of the mental disease, and not merely some irrelevant association.—I am, etc.,

Dumfries. Martin Roth.

Old Age

Sir,—I fear the wording of one or two phrases in my letter on old age (October 1, p. 758) was unfortunate. Naturally I was speaking to my colleagues, and all doctors know that euthanasia is not allowed. In any case, I no longer believe in it, as I am a Catholic. The mention of it was meant to be more in the nature of a query to other doctors—especially non-Catholics—as I am anxious to know their point of view about selfish and apparently useless old people.

But there are other, and kinder, and easier ways, surely, of dealing with such cases. One I mentioned was segregation—and here I would advocate the formation of another society—there is room for one—a society governed by a panel of a few doctors, clergy, and one or two barristers. Let this panel have authority to deal with the cases of hardship and frustration mentioned. Cases could be reported to the panel, or the down-trodden victims could consult it. Further, this panel should have authority to order segregation or other treatment. There are plenty of big, roomy rectories which the occupiers would be only too glad to vacate.—I am, etc.,

Portsmouth. J. Rushworth Lund.

Sir,—I hope you will take up Dr. Lund's challenge (October 1, p. 758). Must we for ever, as a profession, pass by on the other side? Over 75, we become increasingly conscious that we are cumberers, but how can we combine effectively to express that point of view and get the co-operative help of those who bear the burden and heat of the day?

The last twenty-five years have shown how public opinion can change in such a matter as a general acceptance of cremation, for example. Must voluntary euthanasia be for ever "impossible" for serious discussion without such a prefix as "brutal" being applied to it?—I am, etc.,

"Seventy-nine."

Sir,—A letter by Dr. J. Rushworth Lund appeared in the *Journal* of October 1 (p. 758) entitled "Old Age." Many like myself must have read it and no doubt asked themselves the same questions that occurred to me. (*a*) Is the letter intended as a joke? (a poor one admittedly). (*b*) Is it merely a flippant response to the spate of enthusiastic articles on geriatrics? (*c*) Is it a bait to stimulate correspondence on the many problems concerning old age which are on the *tapis* at the moment as a result of recent legislation on health and welfare? (*d*) Could it, by any possibility, be meant to be taken seriously? I confess I do not know the answers to these questions.

It is, however, well that we should accustom ourselves to the idea that we are an ageing population, that the proportion of elderly persons to the wage earners has greatly increased. All the implications of this are by no means fully recognized. We need not, however, disturb our minds with erroneous ideas as to the selfishness of the old or that "so many live only for themselves," for we know better. Selfishness is inherent in all of us. From the moment we are born we are selfish. If we are spoilt in childhood and not trained to resist such impulses the fault grows in us, and if in adult life the spoiling goes on, as sometimes happens, then probably it will last into old age. For this we must not blame the old but rather pity them. Such persons are rarely happy, and who are we to sit in judgment on the faults of our neighbours? Some, it is true, may be a thorn in the flesh of those to whose lot it falls to look after them, but thorns are an essential part of life.

As to the question, "Why encumber they the ground?"—the only answer is yet another question, "Why encumber *we* the ground?" To question one corner of the plan of life is to question it all.

As to euthanasia, it is only when one reads a letter of this type (and maybe it was after all only a joke) that the hideous possibilities of such procedures suggest themselves to one's mind.—I am, etc.,

E. M. Hickey.

*** Several other correspondents have written to express their disagreement with Dr. Lund's earlier letter. This correspondence is now closed.—Ed., *B.M.J.*

B.M.A. Tuberculosis Group

Sir,—With the setting up of the Tuberculosis Group of the B.M.A. there are a number of urgent matters needing consideration. For many years the profession has played with the problem of the prevention of human tuberculosis of bovine origin. Dr. J. Arthur Myers[1] has claimed, "The control of tuberculosis in cattle, therefore, has markedly reduced the incidence of tuberculosis infection, the morbidity, and the mortality from tuberculosis in man." To-day only 16% of our cattle herds are certified free from tuberculosis. It is time that pressure was put on the Government to complete this eradication of bovine tuberculosis within a fixed date.

The next question that requires careful consideration is that a proper critical examination should be made and published of the results of treatment in all public sanatoria. Radical changes in our present methods for controlling this disease may be found necessary. The association of cancer of the lungs with tuberculosis in the lungs or in some other organ of the body is also worth investigating.—I am, etc.,

Itchingfield, Sussex. Sydney Gordon Tippett.

Reference

1 "Bovine Tuberculosis Eradication in the United States and its Resulting Beneficial Effects on Human Health." *Proceedings of the United States Livestock Sanitary Association*, 1941.

Men, Machines, and Materialism

Sir,—Inevitably there arise in the tides of men's affairs issues which demand attention. Wars and their accompanying problems call for direct action, and commonly the men and the means are found and the resources of the people are urgently deployed. There follows almost inevitably a period of relative exhaustion and uncertainty. With these phenomena we are familiar. With the threat of physical extinction or subjection we have grappled not once but again, and with a remarkable unanimity and singleness of purpose. To minimize the eroding effect on a civilization of two major wars in one generation would be futile, but the contemplation of certain human trends—trends which display the "inevitability of gradualness" and a malignant persistence—cannot fail to be gravely disturbing.

Two recent publications in your own columns have met and faced the most disquieting of these problems.

Professor Geoffrey Jefferson, in his Lister Oration (June 25, p. 1105), has assessed the value of the concepts embodied in Dr. Norbert Wiener's book *Cybernetics* and appraised the use of the varied analogies there propounded; but he sees "danger threatening—that of anthropomorphizing the machine," and ends by ranging himself with the humanists. Dr. F. M. R. Walshe, in his letter (August 13, p. 383) inveighing against the most recent example of "materialism" within our own gates, sees us being led "from the free status of a learned profession to that of a sub-group of that drab and alien abstraction 'economic man.'"

Not the least of our perils lies in our own approach to this spreading cult of materialism. Scientific method induces us to weigh and to analyse evidence and motive, and there is a compelling charm in these procedures which may blind us to the fact of our essential humanity and to the existence of the "incommunicables" which go to make it. Study of the computing machine and allied mechanisms may help us to greater understanding of those cerebral mechanisms which are explainable in such terms, and "analysis" (in the psycho-analytic sense) has afforded and may continue to afford us greater insight into the motivation of human behaviour. But the "analytic situation" and the "mechanistic analogy" may assume disproportionate significance, and paralysis of action with spiritual sterility ensue.

Other disciplines than ours stand thus imperilled. Professor F. H. Ayers (*Reflections on Our Age*) has shown how philosophy has long concerned itself with the minutiae of human conduct and endeavour but finds that though the "aims of philosophy" may be to discern how men ought to live there is as yet no common agreement how they should. So may the web become denser, the skein more tangled, and thus persist "the always frustrated struggle of human contrivance relying on itself" (Charles Morgan, *The River Line*).

There, Sir, I submit, lies the challenge to-day. The liberal profession of medicine no less than any other can refuse this challenge, can acknowledge the advance of materialism, can go with the tide. It may be argued that this conflict has progressed too far. I would remind you that the epic actions have always been fought by the rearguard, as at Roncevaux and at Thermopylae. To refuse the challenge is not to court defeat; it is to accept it.—I am, etc.,

Taunton, Somerset. R. SESSIONS HODGE.

St. Luke's Day

SIR,—The eighteenth of October is St. Luke's Day. On that day Christians in all parts of the world commemorate the patron saint of the healing profession. They recall with gratitude the gospel that he wrote for his fellow men. On that day the Church recalls with thankfulness the fact that this physician was called to be "an evangelist and physician of the soul," and prays that "by the wholesome medicine of the doctrine delivered by him, all the diseases of our souls may be healed." That is indeed a consummation devoutly to be wished. Let us study these prescriptions for the soul of a world, sick nearly to death, which this physician had learned from the Master and has preserved for us. In these latter days modern scholarship, and modern translations of Luke's Greek manuscript, give us the opportunity of understanding better perhaps than preceding centuries these prescriptions for a new way of life and health for a sick world. Was Renan right in calling this small book of this Gentile doctor "the most beautiful book we possess . . . a book full of joy"?

It is a pen portrait by a literary artist of the human Jesus Christ: of a man fond of little children; the champion of the cause of women; the Rabbi who welcomed women as his disciples; the friend of hated Quislings and notorious sinners shunned and neglected by the orthodox of his day; the Teacher who could remake these wrecks of humanity, transforming Quislings into true patriots and great sinners into saints, converting Matthew the tax collector to Matthew the scribe of the Kingdom, and Mary of Magdala to be Mary Magdalene, first witness of his resurrection to his chief apostles. This joyful book of Luke's is full of the joy of lives that seemed failures, hopeless failures, transformed to be happy and successful beyond all belief. And this miracle was effected by love—forgiving, understanding love, such as the world had never witnessed. Luke's own closest friend and colleague in his later life was perhaps the greatest case of this incredible marvel—Saul of Tarsus, the arch-persecutor of the early Christian church, the narrow nationalist Pharisee, transformed into Paul the devoted missionary of Christ to the Gentile world. And Luke's second great book, *Acts of Apostles*, is devoted to recording the work of Peter and Paul, both of them failures—transformed, both of them, by the resurrection of Christ, to become His messengers-in-chief to the world—both of them dying, if the tradition be true, as martyrs for "the gospel" at Rome.

Can the present sickness of the world's soul be remedied, or is it past redemption? It is the message of St. Luke (and St. Paul) that it can be remedied—that the world's sick soul can be cured. But only by the medicine prescribed by the Master Physician as recorded by St. Luke and his colleague St. Paul, in the gospel and *Acts of Apostles*. And the "active principle" of this "medicine" is derived from the historic fact of the resurrection of Jesus. That is the astounding climax to which Luke's first "treatise" leads, making sense of Jesus' mission and message to the world. Surely our mammon-ridden, warweary world to-day needs the "wholesome medicines" prescribed in the *Gospel of St. Luke* and *Acts*: "You cannot serve God and Mammon," and "Remember the words of the Lord Jesus when He said, 'It is happier, more blessed, to be giving than getting.'"—I am, etc.,

Banstead, Surrey. HERBERT CAIGER.

Sensitivity to Streptomycin

SIR,—Dr. M. C. Wilkinson (September 24, p. 707) sets out some of the problems associated with the development of streptomycin sensitivity in nurses. He adds that by reporting experiences some way of protecting persons sensitive to streptomycin may be found. I therefore briefly report a case of streptomycin sensitivity to illustrate some other aspects of the problem which this condition presents.

Eleven months after commencing handling and administering streptomycin, a nurse, aged 43, with menopausal symptoms and of neurotic disposition, developed puffiness and itching of the eyelids. This was thought to be due to a local condition, but no local cause was found. Four weeks later the realization that the condition might be due to streptomycin sensitivity led to the carrying out of a patch test. This gave a strongly positive reaction. The chemosis of the eyelids increased and she felt unwell. She was at once removed from work involving the handling of streptomycin, she was given "anthisan" by mouth, and the condition cleared up within a week.

Four months later the swelling of the eyelids recurred, and in addition there was flexural dermatitis of both elbows. Interrogation revealed that she had recently been handling soiled linen which included napkins belonging to children receiving streptomycin for tuberculous meningitis. Once again the condition was controlled by removal from the apparent source of contact and by the administration of anthisan by mouth. Three months later a dermatitis appeared on the wrists and hands as well as the other areas previously involved. A month later, two days after commencing the use of a simple ammoniated ichthyol ointment to the eyelids, a severe chemosis of the lids occurred which subsided on stopping the use of the ointment. The dermatitis remained quiescent for a period of two months until recent weeks. Now, ten months after the first manifestation, a widespread contact dermatitis involving the forehead, neck, eyelids, elbows, wrists, and hands has occurred necessitating her being put off duty. Anthisan is now ineffective.

This case illustrates several points. As in Dr. Wilkinson's first case, the original manifestation of the sensitivity was in the eyelids and not on the hands as would be reasonably expected. In the second place, protection by wearing rubber gloves whilst handling streptomycin solutions may give a false sense of security if no protective measures are employed when other sources of contact such as soiled linen are handled. Most important of all, when sensitivity develops it is a very distressing and incapacitating condition which appears to persist after all obvious sources of contact with streptomycin have been excluded. This raises the question as to whether development of streptomycin sensitivity predisposes to sensitivity to other

agents. The fact that the development of streptomycin sensitivity in a nurse may accentuate the already critical shortage of tuberculosis nurses is a side-issue of no little importance.

I wish to acknowledge the help given by Dr. R. Aitken, Dr. G. A. G. Peterkin, and Dr. J. Macaskill in this case.

—I am, etc.,

Edinburgh. N. W. Horne.

Massage with Adrenaline

Sir,—My attention has been drawn to a letter by Dr. G. L. Foss on this subject (October 8, p. 816). I wish to point out that the circular to which he refers has no connexion with my article (*Medical World*, April 15, 1949). In it no suggestion was made of any relation between the adrenaline-cream treatment for chronic rheumatism and Kendall's "compound E," and the treatment of rheumatoid arthritis was not even mentioned. I wish especially to disclaim any association with, or knowledge of, the pamphlet to which Dr. Foss refers.—I am, etc.,

London, W.1. Louis Moss.

Simulated Amnesia

Sir,—May I point out to Dr. Harold Palmer (August 27, p. 487) that I have put forward and fully discussed the contention that malingering only occurs in the hysterical personality (*Psychiatry, A Short Treatise*, 1948, Bristol, pp. 109 and 115)? This would appear to agree on all major points with his remarks in his letter. Malingering as a psychiatric notion should be discarded, as it carries a definite legal implication. From the medico-legal point of view it is unlikely that a diagnosis of hysteria would in any way distort the judgment of the courts in favour of an evildoer. Society cannot be expected to pay for the behaviouristic experiments of the so-called malingerer, of the hysteric, or of the psychopathic personality. By discarding the term "malingerer" no harm would therefore be done, while the integrity of psychiatric nomenclature would be preserved.—I am, etc.,

Kingswinford, Staffs. W. A. O'Connor.

Hypnosis in Treatment

Sir,—I am glad that my letter (September 17, p. 653) has stimulated some interesting views on hypnosis. However, I remain far from being reassured about its possible dangers.

Dr. Neville Murray (October 1, p. 756) admits that my postulates are correct in part, while the other parts of the whole remain among the great unknown imponderables. He mentions the Rorschach test as being one which gives objective evidence of personality structure. Although I have no experience of it, I believe that it works on the principle of the ink-blot test, and I would be surprised to find it more than a rough measure, which is difficult to assess and judge, apart from the preconceived ideas of the widely differing schools of psychology or from the subjective personality of the examiner. While some aspects of personality are rightly the concern of psychology, we cannot concede that other scientific and human disciplines should not be entitled to an equal or greater concern. Lastly, he makes an inaccurate presumption as to conceptions I am supposed to hold—I used the word "influence"; he uses the term "mental assault."

Dr. A. P. Magonet (p. 756) also makes an inaccurate presumption in stating that I believed hypnotized subjects to be "passive automatons." Fortunately there are limits to what even they will accept in the way of suggestion; we all know that well enough. He cites the case of a girl with cardiospasm who could not swallow the fact that her mother had died. This presupposes that the girl was intellectually capable of conceiving a symbolic idea containing a high degree of abstraction.

Symbols of this kind are all very well for the highly educated, but symbols in general are originally spontaneous and relevant, unless the subject is very suggestible and the idea is implanted from outside, which may well have been the case in this patient. Death is associated with ritual eating admittedly—e.g., wakes and the now extinct sin-eater—and we know something about the history of such practices. They are considered to be inappropriate to modern thought, but may be the basis of this symbol. The fact is that two separate events occurred at the same time with all probability of causal connexion. The nexus might consist of a symbol but might also be of a different nature altogether—e.g., a chronic manifestation of the swallowing difficulties some of us have felt in acute form while awaiting viva voce examinations. In this case feelings of emotional insecurity at the mother's death would give rise to the state of chronic anxiety, only understood in part by the patient, whose attention is concentrated on the symptom.

Under hypnotism, with the critical faculties depressed voluntarily even if not altogether in abeyance, it is likely that a variety of more or less plausible explanations would be acceptable. If the explanation is accepted by the patient in a case of that sort the symptom may disappear. So it has always done over the face of the globe and for many centuries.

Such examples do nothing to alter my conviction that the more widespread use of hypnotic methods for symptoms arising in patients not generally considered to be hysterical brings possibilities of dangers to the personality not at present realized. The fundamental criticism of hypnosis is an urgent need and must come from abler people than myself, as I have already suggested. Until more is known of its nature and long-term effects its use should be limited.—I am, etc.,

Birmingham. K. M. Hay.

Treatment of Early Pulmonary Tuberculosis

Sir,—The position regarding the treatment of early pulmonary tuberculosis is still deplorable. In my area it is usual for a patient to be told that he may have to wait for six months or more before being admitted to a sanatorium, even though he be a young person with an early lesion. Domiciliary treatment is handicapped by the fact that there are too few tuberculosis medical officers to help with the work.

If general hospitals were asked to deal with a sufficient number of these patients to reduce the sanatorium waiting-lists to a few weeks they would find that their own waiting-lists for other patients would be impossibly long.

I suggest that the B.M.A. approach the Minister of Health with the object of finding ways and means of providing more beds for the treatment of these cases. This would mean opening hospitals now closed for one reason or another, building others, and attracting staff to them by means, perhaps, of higher pay. This should have priority in the N.H.S., even if this means greater economy in some other parts of the Service.—I am, etc.,

Dorchester, Dorset. J. Herbert-Burns.

Manipulation for Low Backache

Sir,—Dr. N. B. Eastwood's letter on manipulation for rheumatism (September 24, p. 710) will probably stir many doctors to action, either mentally to contradict or manually to try their hand. Dr. Eastwood must be congratulated on manipulating his cases of low backache, for this takes considerable time in a busy practice. That it is the correct thing to do I am in no way in doubt, especially as soon as possible after it is first reported. That at least three-quarters of his patients benefited considerably is very satisfactory.

Two of his statements, however, invite criticism. The title of his letter continues to breed confusion of thought. The low backache and not rheumatism is the complaint and reason for manipulating. It is this pain in the back or buttock or the constant ache that the patient complains of. The doctor should not call it rheumatism or fibrositis. That the diagnosis is "probably of articular origin" is not in doubt by those who manipulate, but to state that the manipulation "appears to act on the sacro-iliac joint" is quite incorrect. The cause of low backache has been conclusively shown by many authors to be due to derangement of a lumbar intervertebral joint in the majority of cases. The sacro-iliac joint can easily be tested and excluded as a cause.[1]

The manipulation described is interesting but complicated. It can more easily be performed on a couch in comfort, with two or three variations should improvement not take place.[1,2]

The principle of the manipulation described is probably quite incorrect. The essential points are that some flexion of the lumbar spine and rotation at the same time be maintained and augmented momentarily by excessive rotation. The partial flexion is essential in that the posterior aspect of the intervertebral joint is widened, so as to allow the nucleus pulposus to return to its correct place. When extension is attempted on these cases it frequently temporarily aggravates the condition.

Before manipulation is attempted in cases of low backache it is hoped that the patient is carefully examined systematically, testing all spinal movements, sacro-iliac joints, hip-joints, and muscle strength of both legs, not forgetting the abdomen and a rectal or P.V. examination. Otherwise indiscriminate manipulating for low backache will be disappointing and patients will not grow to trust the doctor who manipulates. With experience and practice it is a most essential accessory to one's armamentarium.

In my experience manipulation is the only preliminary treatment of any value in a deranged lumbar intervertebral joint in the right type of case. Manipulation should always be followed up by extension exercises of the trunk. In those cases in which recurrence is frequent epidural injection or a lumbar corset may help.—I am, etc.,

Ryde, Isle of Wight. TREVAN HAMBLY.

REFERENCES

1 Cyriax, J., *Rheumatism and Soft Tissue Injury*, 1947, London.
2 *Handbook of Osteopathic Technique*, 1941, Los Angeles.

Locked Twins

SIR,—The purpose of this letter is to place on record a patient who had locked twins at Rosedene Maternity Hospital, Inverness, in March, 1949.

The patient, a 19-year-old primigravida, had been under observation in hospital for six weeks prior to delivery because of pre-eclamptic toxaemia. Pre-natal *x*-ray examination showed twins, one of which lay as a vertex and the other as a breech presentation. Labour started spontaneously at the 37th week and followed a normal course. The first infant, a breech presentation, delivered spontaneously to the neck from the left sacro-anterior position. Vaginal examination now revealed that the head of the second foetus was well down in the pelvic cavity in the left occipito-posterior position with the head of the first still at the pelvic brim. Attempts to disengage the infants were unsuccessful, and by the time specialist aid could be summoned the first infant had succumbed, so it was decapitated and, the second bag of membranes having been ruptured, the second baby was gently extracted with the forceps. The head of the decapitated infant was then delivered by passing the middle finger into its mouth, the other fingers protecting the uterus from damage by the severed vertebral column. The extraction was accomplished by traction and suprapubic pressure. After a normal third stage, inspection of the placenta proved it to be of the uniovular type. The infants were both males weighing respectively 4 lb. (1.81 kg.) and 4 lb. 1½ oz. (1.85 kg.).

—I am, etc.,

Inverness. JAMES W. DAVIDSON.

Treatment of Cutaneous Anthrax

SIR,—The description of the diagnosis and treatment of cutaneous anthrax by Drs. John A. Holgate and Reginald A. Holman (September 10, p. 575) should not pass without comment. Northampton, a centre of the leather industry, has a fairly steady incidence of cutaneous anthrax, and I have been responsible for the diagnosis and have followed the treatment of some 20 cases during the last eight years.

On admission the patient is given 0.45 g. of "stabilarsan" and 100 ml. of serum subcutaneously. A second 100 ml. of serum is given later if the clinical condition of the lesion warrants it. With this treatment recovery has always been uneventful. Two cases, however, were treated with penicillin. Both developed a sharp rise of temperature shortly after the injection, and there was a great increase in inflammatory reaction around the lesion. The condition of the patients deteriorated, and it was considered necessary to administer amounts of serum greatly in excess of those normally used. The penicillin appeared to be responsible for the unusual severity of these cases and its use has since been abandoned.

I would suggest that penicillin causes a sudden destruction of a large number of anthrax bacilli, with a liberation of endotoxin which increases the local inflammation and causes pyrexia. The literature on the treatment of anthrax by penicillin suggests that the disease is of great severity and danger, and that vast doses of penicillin are needed to control it. In our experience cutaneous anthrax is not a severe disease and is easily controlled by the use of serum and stabilarsan. Intravenous injection of the serum is rarely necessary or desirable. May I suggest that in their next series of cases Drs. Holgate and Holman treat alternate cases with and without penicillin, when I feel sure that they will soon abandon its use.—I am, etc.,

Northampton. L. HOYLE.

Treatment of Ringworm of the Scalp

SIR,—The paper by Drs. H. Haber and R. T. Brain and Mr. J. W. Hadgraft on the treatment of ringworm of the scalp (September 17, p. 626) raises many important questions, particularly in connexion with the mode of action of preparations containing fungicides. Since similar results were obtained with phenylmercuric nitrate and with salicylanilide, it is deduced that "it is not the fungicide which effects the cure but the penetrating power of the bases employed" (carbowax in the cases described).

This view is not, however, in accordance with the results we have obtained in a recent investigation concerned with 261 cases of ringworm of the scalp due to *Microsporon audouini*. Using three different fungicides in carbowax, cures ranging from 38% to 74% were recorded. The mode of action of fungicides is undoubtedly complex, and whether treatment with such compounds is necessary after *x*-ray epilation is controversial. Brain and his colleagues state that "*x*-ray epilation has to be followed by the application of a fungicide." Lydon, Stephanides, and Robb[1] have reported cures in 103 cases by *x*-ray epilation without the application of fungicides. We are fully in agreement with the statement that the hair itself resists penetration of reagents, but we have not been able to find evidence that carbowax is capable of softening the hair or loosening the connexion between the hair and the hair papilla.[2]—We are, etc.,

A. J. E. BARLOW.
F. W. CHATTAWAY.
C. S. WHEWELL.

Huddersfield.

REFERENCES

1 *British Medical Journal*, 1949, 1, 523.
2 Barlow, A. J. E., Chattaway, F. W., and Whewell, C. S., *Brit. J. Derm. Syph.*, 1949, in press.

University Degrees

SIR,—I have been most interested in the views expressed by your correspondents on medical education, and wonder if you would consider printing some comments from a London clinical student who held senior officer rank in the late war and is somewhat older than his fellows.

While agreeing that the present multiplicity of qualifying degrees and diplomas, all of them more or less of the same standard, is most illogical and should be simplified, it seems a lot to hope that the universities, colleges, etc., will settle their differences before the Greek Calends, and meanwhile the non-university student graduating into the National Health Service is seriously handicapped.

I refer to the point (brought out by one of your correspondents) that none of the higher appointments in the profession, as it is at present being reorganized, is open to those who do not hold the M.D. or M.S. *in addition* to the M.R.C.P. or F.R.C.S. Now, although the university graduate is allowed by the Colleges to sit for the membership or fellowship without insisting that he take all their previous examinations, the qualified Conjoint man must in the case of London University (whose external regulations are the least exacting in this respect) go back to dissecting a frog and doing elementary physics and chemistry and all the other examinations for the external M.B. before being permitted to sit for a higher degree. There must be few indeed with either the time or money to waste in performing such a feat, and surely it is questionable whether it is desirable to employ a qualified man's time in undertaking such a pursuit.

On the other hand, I quite understand the natural reluctance of any university to cheapen its higher degrees—it would both lower the standard and discourage people from taking the initial M.B. But at the same time it must be admitted that it is very unfair for the brilliant Conjoint student to be perpetually condemned to a secondary position *vis-à-vis* his university colleagues as far as senior hospital appointments are concerned. This point, I should like to stress, has arisen in a particularly acute form since the institution of a service where higher degrees and diplomas are going to win promotion to the highest posts and which we should all enter without handicaps and with equal chances for our talents.

I therefore beg to suggest that London University (let it be hoped soon followed by others), through its national position and the fact that it possesses an external department, should take the lead in allowing any man or woman qualified in this country who is a matriculated student of the university and has spent at least three years in a medical teaching institution approved by the university to take a qualifying examination, which might consist of part or the whole of the M.B. finals, and which would in no sense confer a degree in itself but would allow successful candidates to go up for a "special" M.D. or M.S. degree later.

I feel that this might be a reform which could be put through with the least disturbance to existing institutions, and therefore that it might stand some likelihood of being adopted in time to be of some use to the students of to-day (many of them non-university simply because they are ex-Service), who feel a sense of frustration at qualifying into a nationalized profession with the highest posts permanently denied them however keen or able they may be.—I am, etc.,

London, S.W.3. E. O'C. Tandy.

Cigarette Cough

Sir,—I wonder if any of your readers have any views to express on the above subject. I have frequently been called on to differentiate between genuine cigarette cough and cough symptomatic of disease, and have found the following points of considerable help.

(1) A cigarette cough, though it sounds distressing, especially when well established, does not cause any distress; as soon as a fit of coughing is over the subject continues to breathe quite normally and without any noticeable acceleration of the respiratory rate. (2) Though the cough may have a moist quality it is not usually productive, unless the subject has a cold or other catarrhal condition of the respiratory tract. (3) The cough is invariably brought on by the first cigarette in the morning. (4) It is noticeable that very many heavy cigarette smokers who inhale steadily have little or no cigarette cough, while very frequently non-inhalers are severely afflicted. I believe that this is explained by the fact that non-inhalers are more prone to the habit of leaving the cigarette in the mouth while smoking. This means that while they may not inhale the filtered smoke pulled through the cigarette they are continuously inhaling the hot, unfiltered smoke trailing up from the tip, the irritant nature of which will be appreciated by anyone who has had the misfortune to sit beside an inconsiderate smoker at the pictures or the theatre.—I am, etc.,

Cavan, Eire. B. J. Gallighan.

Diabetes and Gout

Sir,—Your leading article on diabetes and gout (September 24, p. 692) contains certain questionable statements which might mislead some of your readers. It is said that "in 1909 Ascoli and Izar showed that dog's liver contained an enzyme which converts uric acid to dialuric acid, so that probably uric acid can be converted into dialuric acid in man." The facts, however, are that dogs possess an enzyme, uricase, which converts uric acid into allantoin, but that neither this nor any other uricolytic enzyme is present in human tissues, which are unable to convert uric acid into any other substance.

Regarding experiments on birds, pigeons are alleged to have died "from a deposit of sodium urate over all the serous surfaces." Surely the inference should be that an inflammatory condition of these surfaces was associated with deposition of urates on them, but the cause of death is not evident. In general, results obtained for one species, or even sub-species, of animal cannot safely be extrapolated to other species, and this is particularly the case for purine metabolism. While there certainly appears to be a case for connecting rheumatoid and possibly gouty arthritis with steroid metabolism, the evidence presented is insufficient to establish any connexion between human diabetes and purine metabolism.—I am, etc.,

London, N.W.6. R. Truscoe.

Dysentery in Monkeys

Sir,—Until recently monkeys intended for experimental work were of necessity imported by sea. Recently, however, large numbers of the common rhesus monkey, *Macaca mulatta*, have been imported by air from India, and many have been re-exported to the U.S.A. after only a few days in this country. A high mortality among the animals was usual during the sea voyage, but this is much reduced by air travel. By this route a death rate of 2% is considered high by the airway companies.

However, the shorter time spent on the journey implies that a higher proportion of sick animals arrive in England, and some may well be carriers of infectious disease. Recently we have seen three outbreaks of clinical dysentery in such monkeys awaiting re-export and have isolated from them *Shigella flexneri* type 103 Z, as reported by us from these animals in 1948.[1] Another animal with the same infection was procured from a commercial dealer, but its method of import was not stated. From yet a fourth outbreak we have isolated *Shigella schmitzii*. Human infection with *Shigella flexneri* type 103 Z is rare in this country, but it appears to be more common in the U.S.A. However, we feel that a hazard exists. Spread of *Shigella schmitzii* from apes to their keepers was recorded by one of us in 1949.[2]

British Overseas Airways Corporation are fully cognizant of this matter and have already instituted control measures, both on the aircraft and at airports, to prevent any spread of such infections either to the aircrew or to those handling the animals during loading and unloading or while tending them during any stops.—We are, etc.,

R. E. Rewell,
Zoological Society of London.
R. F. Bridges,
Dysentery Reference Laboratory, Oxford.

References

1 Rewell, R. E., and Bridges, R. F., *Mon. Bull. Min. Hlth*, 1948, 7, 25.
2 —— *Lancet*, 1949, 1, 220.

POINTS FROM LETTERS

Resisting Pain

Dr. R. Macdonald Ladell (Edgbaston, Birmingham) writes: Mr. Charles Davy's comment (September 24, p. 709) on the excellent article by Dr. E. B. Strauss (August 20, p. 411) reminds me that a few years ago I embarrassed my dentist (since deceased) by insisting that he should draw four well-rooted molars in succession without using any anaesthetic whatever. I am not a masochist. My main reason was the spiteful one that I heartily disliked the dentist as a man, though respecting his professional abilities. Every psychologist will appreciate that point. My other reason was to test my theory that pain when understood and accepted because it serves some end can have a tonic effect. Certainly I experienced no sense of shock and came away with a sense of well-being. This last of course may have been due to the fact that I was feeling pleased with myself. Is it not possible, however, that we make too much of a bogy of pain?

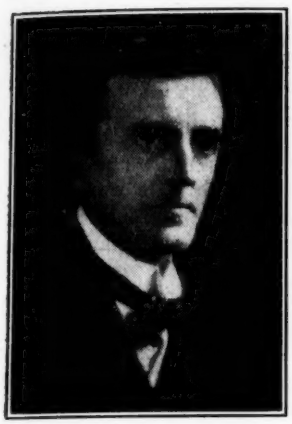
The Use of Experience

Dr. David Wheatley (Twickenham, Middlesex) writes: In his article (September 24, p. 663) Sir Heneage Ogilvie rightly condemns the narrowness of outlook which may be produced in some by specialization. Yet does he not fall into the same error himself? Later, referring to the hollow needle, he observes that "it must bear the responsibility for spinal anaesthesia." This would seem to reflect upon the latter procedure and must surely be a personal opinion. And would he agree that the woman with severe hyperemesis gravidarum, to quote but one example, is "rejecting what is harmful or surplus to requirements [of her tissues]"? Even taken in its context I find it hard to reconcile such a sweeping statement with the objects of the article, although I may be biased through reading it with a physician's outlook.

Obituary

MAJOR GREENWOOD, D.Sc., F.R.C.P., F.R.S.

Major Greenwood, professor emeritus of epidemiology and vital statistics in the University of London, who died suddenly in London in his seventieth year, on October 5, was for more than a generation one of the outstanding figures of the day, both in his chosen field of medicine and among statisticians in this country and throughout the world. Though there is no doubt that he became the leading authority on medical statistics, at such a description he might himself have smiled sardonically, for throughout his career he was no respecter of authority, no lover of "expert witnesses," no accepter of *ex cathedra* statements. Indeed, in a somewhat "left-handed" way he had an abiding affection for the amateur in science, the amateur with no reputation and no technical tricks at his command, but with a questioning mind, a fund of common sense, and above all an intellectual honesty of purpose. It was such characteristics, probably, that made so dear to him John Graunt and his "shop arithmetic" on the seventeenth-century bills of mortality, and at a later date his great hero William Farr, who with the simplest of approaches built so firmly our English system of vital statistics, and so equally simply displayed its value. Though an able practical mathematician, Greenwood never lost this love of simple statistical tables or of what he himself invariably called "little sums."



Major Greenwood was born in 1880, the only son of a general practitioner in the East End of London. He was educated at Merchant Taylors' School, from which he went for his medical training to the London Hospital. On qualifying in 1904 he was appointed demonstrator of physiology in the London Hospital Medical College, where Leonard Hill had taken up the professorship. Here he was associated with Hill and his early work on caisson disease. During these years his mathematical leanings led him to University College, London, to study the then newly developing science of mathematical statistics under Karl Pearson. For these two men of international and lasting reputation, masters in very different fields of science, Greenwood never lost his early feelings of admiration and attachment. With both medical and statistical crafts now at his command he was in 1910 appointed statistician to the Lister Institute, and began to publish the long series of studies of vital statistics which were the foundation of his later career—studies, for instance, of infant mortality, of marital infection in pulmonary tuberculosis, of hospital mortality rates from pneumonia. Here, too, he made detailed investigations of the epidemiology of plague in India, working alongside Arthur Bacot, one of his most intimate friends, whose early death was a blow from which he never wholly recovered. Though on the staff of the Lister Institute till 1919, the first world war naturally redirected his activities. He took charge of a medical research subsection of the Ministry of Munitions and became immersed in the problems of hours of work, of the dietaries of munition workers, of the incidence of tuberculosis in the industrial community, and, lastly but probably the most remembered to-day, the incidence of repeated accidents in factory workers or what became known as "accident proneness." In this work he collaborated with Udny Yule.

These years led also to his association with Professor E. L. Collis and their joint book, *The Health of the Industrial Worker* (1921), and, more indirectly and some years later, to the Medical Research Council's Statistical Committee, which was a descendant of the wartime committee on the Health of Munition Workers. Greenwood became first chairman of the statistical committee, a position he held till 1948, and, aided by the members of the committee, the Council's statistical staff that he had gathered round him did much to raise the standard in the presentation and use of statistics in medical publications. At the end of the first world war he left the Lister Institute to take charge of medical statistics at the newly established Ministry of Health, where he worked in close association with Sir George Newman, the first C.M.O. Here his deep interest in historical epidemiology became increasingly apparent not only in his published papers but also in many unsigned contributions to Ministry of Health reports which unmistakably bear his mark—for example, that on the 1918 influenza epidemic. How he found time for it all is difficult to see, but he was a man of few interests outside reading, and he read late and early—not only indeed within his subjects but roving over the whole field of literature, modern and ancient, and with a phenomenal memory that allowed him to quote largely and at will—with Latin in the original as a mere sideline. So at this turning-point of his career there were papers on Galen and on Sydenham, on the fertility of the English middle classes and the vital statistics of Sweden, on the natural duration of cancer and the vital capacity of young healthy males, many of these papers, naturally, in collaboration with other workers.

From the Ministry Greenwood moved in 1928 to his final position—Professor of Epidemiology and Vital Statistics in the newly created London School of Hygiene and Tropical Medicine, a chair he held till his retirement in 1945. Here, though in fact its beginnings came a year or two earlier, he entered upon that long and productive phase of work in association with his colleague W. W. C. Topley, the School's professor of bacteriology and immunology, in their study of experimental epidemiology or, as Greenwood once wrote, the attempt "to mould a little epidemiological world of our own nearer to the heart's desire" in the hope of elucidating the laws of the epidemic rise and fall of disease. Though fifteen years of work did not allow them to give a precise quantitative expression to the law of development, it threw much light on epidemic occurrences and on such practical issues as the limitation of protection by inoculation. Here, for example, arguing from mouse to man, it seemed that artificial immunization could be of great value for a short or discontinuous period of even severe exposure but would not avail against a long-continued exposure to a very unfavourable environment. At this time, too, Greenwood developed an interest in the growing subject of psychology, and, collaborating with his colleagues Dr. May Smith and Professor Millais Culpin, both read and wrote thereon. He had also his teaching duties to perform—directed almost entirely to postgraduate students sitting for the University's diploma in public health. In the preface to his Herter lectures, "Epidemiology, Historical and Experimental," delivered in Baltimore in 1931, he expresses his

conviction "that the history of ideas is an essential part of the education of both public health officers and laboratory workers," and this view ran clearly through his lecture courses.

The student in search of "facts," to be transferred from the lecturer's notebook to the student's notebook "without passing through the mind of either," would find Greenwood of little help. He was not at his best either in teaching statistical methods—they came much too easily to him to allow him to appreciate the difficulties of others. But only a very mediocre student could sit through the course of lectures which he subsequently published under the title of *Epidemics and Crowd Diseases* (1935) without feeling an inspiration, a fascination which would long outlast a mere examination. In his final years Greenwood renewed his historical studies—perhaps, like many of us, as a temporary escape from the realities of the day during the second world war. These resulted in his Heath Clark lectures on British pioneers of social medicine.

Major Greenwood was elected a Fellow of the Royal College of Physicians in 1924—he had given the Milroy lectures in 1922; was awarded the Buchanan Medal of the Royal Society in 1927 and elected a Fellow in the following year; was honorary secretary of the Royal Statistical Society from 1919–34, its president in 1934–6, and, in 1945, one of the rare recipients of its gold medal; he served on the Senate of London University and on many of its committees. Many persons who never met him must have known him through his writings, for apart from the flow of scientific papers he wrote many articles and letters in this and other journals. They will have realized that he was a forcible fighter for what he believed to be right, and that his command of epigrammatic incisive English and his satirical wit made him an opponent that no one would lightly seek to provoke. He may thereby have inevitably discouraged some from entering the statistical field, one in which the way appeared so hard—but that is a risk that must be run by every medical statistician with an urge to raise the standard of what Greenwood once called "arithmetic guided by logic." Many others he must have encouraged and inspired, both by his zeal for accurate observation and clear presentation and by his unchanging belief in the importance of statistical methods in medicine, a belief which he lived to see widely accepted.

Sir Robert Hutchison writes: I first got to know Major Greenwood when he acted as one of my clinical clerks at the London Hospital about forty-six years ago, and was at once impressed by his keen intelligence. Although his father had been a general practitioner, he himself never attempted to practise. He felt probably that clinical work was not really his *métier* and he could never have acquired what is called a bedside manner. He took instead to the study of epidemiology and medical statistics, for which kind of work he was well suited by the penetration and accuracy of his mind and by his fondness, as he often put it, of "doing sums." There were some, I know, who thought him cynical and censorious, and to some degree they were right. He certainly had a poor opinion of modern man, and he had too much intellectual integrity to have any patience with stupidity. He could, indeed, be a devastating critic and controversialist, while his voice and expression were apt to make him seem supercilious. Those who knew him best, however, realized that much of his acerbity of manner and lack of geniality was really due to shyness and that he was as stern a critic of his own work as of that of others. It is true that he did not wear his heart upon his sleeve, but to the few whom he admitted to his friendship he was entirely loyal, and would send them long typewritten letters, sometimes weekly, in which he discussed anything and everything in his rather astringent style and with the frequent use of italics which was characteristic of him. Essentially, indeed, he was modest and unassuming; his foes were pretentiousness and pomposity, and these he fought with a rapier-like wit. He was by nature rather melancholy and, since the death of his wife, lonely. When he spent a week-end with me two or three months ago it was evident that he neither wished nor expected to live much longer, so doubtless death came to him as a friend and, as he would have wished, unheralded.

Dr. Millais Culpin writes: Perhaps only Greenwood's intimates could understand his curious blend of formality and good fellowship, and how even his humour demanded the precise word and the rounded phrase. He played a pretty game of chess, failed to reduce bridge to a mathematical formula, and reverenced piquet as the relic of a gracious past. Up to the end he visited a 90-year-old neighbour once a week, to cheer her up by playing with her a card game that only they understood. Unexpected doings like this last surprised those who knew only what seemed a rather formidable academic personality. Some have thought that he selected statistics as his life's work because that branch of medicine was most remote from the emotional. Perhaps they were right; he was a sensitive soul and often found refuge in doing sums, though the human meaning might still intrude. He once said he never knew till he visited that city why the death rate of Ditchworth was so high, but when he came out at the railway station he could see that no one there would wish to grow old. "And," he added, "I explained that to the city fathers before I left." He could be very blunt to his closest friends if he thought the occasion demanded bluntness. Indeed, he might seem to say that because he was one's friend he expected one's standard to be as high as his. He confided to me, after his return from a trip to America where he delivered some academic lectures, that he had scruples about accepting a fee for them. Some of the staff in his department at the School were Civil Servants, not very well paid, and they couldn't take time off for a holiday in the States and get extra money for it, so he was planning a subtle holiday-equalization fund to ease his conscience. He read many books in divers languages and had an old-fashioned facility for the apt quotation. With his literary memories at his command, on a country holiday he could give the stories of most of the people that had mattered in local history, bishops and agriculturists in particular. Although he might spend a week-end with a newspaper lord or go on some public errand to Geneva, he found satisfaction of his social needs chiefly in academic circles, and he had a deep-rooted pleasure in his association with the University of London. In discussing some matter of university policy with me he once said, "Remember, I was brought up in the Hackney Road—and you weren't far off." I had then known Major Greenwood for nearly half a century and I felt that we understood each other.

Dr. Charles Singer writes: I should like to send a tribute to the memory of my old friend and colleague, Major Greenwood. There must be very few members of our profession with such wide accomplishments. Your pages have for many years given evidence of his lively and felicitous style and not least in his article on "A Cholera Centenary," which appeared last week. Greenwood possessed an extremely exact mind. His accurate scholarship gave point—often somewhat painful point—to an exceptionally

ready and often mordant wit. Long ago I learned to regard as final his judgment, when he cared to give it positively, on any point of scholarship. How he succeeded in his busy and academically eventful life in acquiring such facility and accuracy in both mathematical and classical disciplines has always been a mystery to me. His learning had about it an almost uncanny element. It was often my honour and privilege to discuss with him matters of scholarship. I cherish the memory of these many meetings, but most of all I cherish the memory of being associated with him in his establishment of the first organization to assist scholars driven from their homes by the German Nazis. In this most successful venture he appeared at his very best as a humane physician and a lover of every form of learning. Despite his formidable humour, Greenwood was an extremely kind-hearted man and he hated every form of unfairness and injustice. I saw him at his gallant best as the effective mover for the foundation of the Academic Assistance Council (later the Society for the Protection of Science and Learning) in 1933. From that time on he served its cause—the salving of learning in a war-ridden world—with all his might, and he acted as treasurer of the society to the end of his life. He was thus the agent in preserving for civilized posterity the work of innumerable important scholars, thinkers, writers, and scientific investigators. In dealing with the complicated and difficult affairs of these unfortunate carriers of civilization he always showed them the utmost personal consideration, and no trouble was too great for him to take on their behalf. The world of learning owes him a very deep debt. Many hundreds of scholars all over the world will mourn the loss of this great-hearted, far-sighted, valiant little man. His life and bearing have lent a nobility to learning that could not fail to be recognized by all who knew him. The entire intellectual life of the next generation will be the richer for what Greenwood has done for it. He was personally a retiring and rather withdrawn man, and it may be that this great service will be forgotten ; but it was none the less very real and effective, for Greenwood was a most determined and vigilant watchdog of civilization against the attacks of barbarism.

AUGUST KROGH, Ph.D.

Professor August Krogh, the famous physiologist, died on September 13 at his home in Copenhagen. He was 75, and had been ill for some time. Professor Krogh won the Nobel Prize in physiology and medicine in 1920. He had held the chair of zoophysiology in the University of Copenhagen from 1916 until his retirement in 1945.

We are indebted to Sir Henry Dale, O.M., for the following appreciation : In no country outside his own was Krogh more intimately known, or held in higher regard by workers in his own chosen field of science, than in Britain, where he made some of his closest scientific and personal friendships. He was a frequent visitor to this country, and when he came to a meeting of the Physiological Society he came as an ordinary and always welcome member. Krogh did not study or qualify in medicine ; like some of our own most eminent contributors to physiological science, in particular some of the Cambridge school, his approach was from the side of general biology, and without immediate concern for specifically medical problems. It is hardly necessary to add that he was led by that route to studies of the highest medical interest and importance. He graduated at Copenhagen in zoology in 1899, but from 1899 to 1908 he was assistant in the department of physiology of the Copenhagen medical school, under the late Professor Christian Bohr. It was under Bohr that he had his first experience of research and acquired his interest in the study of the blood and of its function as a carrier of the gases connected with respiration. A communication of his work in this field to the International Congress of Physiology at Heidelberg, in 1907, first brought Krogh and his work to wider notice and made contacts for him with the late J. S. Haldane and with his own near contemporary, the late Sir Joseph Barcroft. Krogh's last visit to England, in 1948, was to take part in a conference at Cambridge on haemoglobin and its properties, held to commemorate Barcroft and his work.

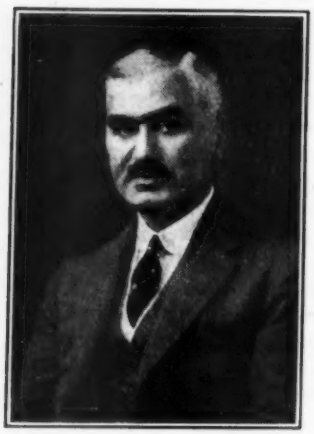
Krogh's activities as a research worker, devoted to physiological problems of many kinds and over a wide range of animal species, have enriched physiological knowledge in a number of its departments. His fundamental work on the contractile and other functions of the capillary blood vessels brought him the award of a Nobel Prize in 1920, and was fully presented in a monograph, embodying his Silliman Lectures at Yale, in 1922. A little later he was concerned with the introduction of insulin to Denmark and the establishment of its manufacture there. He published other monographs on osmotic regulation in aquatic animals and on the comparative physiology of respiratory mechanisms. Having retired in 1945 from the university chair of zoophysiology, which he had held since 1916, Krogh was given a special appointment and provided with a small research establishment in the basement of his house in Gentofte, in the environs of Copenhagen. Here, until his last illness, he was happily at work in a relatively new field of investigation dealing with the special physiology of insects. For this purpose he was receiving a regular supply of live locusts by airmail from the international research centre on locust control in our British Museum of Natural History at South Kensington. To study the contractile activity and metabolism of locusts in flight he had constructed a light and delicately pivoted merry-go-round, which could be driven by the flight of attached locusts in such rapid rotation that they could be observed only by stroboscopic illumination. The work was already yielding new and important items of physiological knowledge, and it is sad to think that the guidance and inspiration of Krogh's special genius should be lost to it at so early a stage.

Krogh received many public recognitions, including several from Britain. The Royal College of Physicians of London awarded him its Baly Medal, while the Royal Society made him one of its limited group of Foreign Members in 1937 and appointed him to give its Croonian Lecture in 1940, though the war prevented its delivery till 1946. Krogh had a quiet and rather shy personality, with a jerky manner which did not obscure his warm friendliness or his ever ready response to humour. Like all loyal Danes, he suffered greatly in spirit under the German occupation, though, more fortunate in that than some of his colleagues, he escaped direct or physical ill-treatment. The experience seemed to make him only the more eager to renew ties of international friendship, and especially those with colleagues in Britain, by whom his memory will long be cherished in affection and esteem.

ROBERT MILNE, M.D., M.S., F.R.C.S.

Robert Milne, consulting surgeon to the London Hospital, died suddenly while on holiday on September 29 at the age of 68. He was born in 1881, son of Dr. Robert Milne, of Inverurie, and educated at the City of London School, joining the London Hospital as a medical student in 1899. In addition to an entrance scholarship he carried off scholarships in anatomy, physiology, and chemistry as well as many prizes. He qualified in 1904 and graduated M.B., B.S. a

year later, proceeding M.D. in 1907. After qualifying, Robert Milne held practically every house appointment there was to hold, house-physician, house-surgeon, receiving-room officer, resident accoucheur, with in addition assistantships in the departments of pathology, ophthalmology, oto-rhinolaryngology, and orthopaedic surgery. On this solid foundation of general training, and after taking the F.R.C.S. in 1906, he began, with his appointment in 1908 as surgical registrar, to build his surgical career under the aegis of Rigby and Furnivall. Appointed assistant surgeon to the London Hospital in 1910, he was surgical tutor and teacher of elementary clinical surgery from 1914 to 1920. During the 1914–18 war he served as a major in the R.A.M.C. in France and Italy. In 1922 he became a full surgeon to the hospital and assumed responsibility for the orthopaedic department—and with it the mantle of "Tommy" Openshaw. Between the wars, in addition to a busy consulting practice he was constantly in demand in the courts for an opinion in accident cases. He was consultant surgeon to Dr. Barnardo's Homes, a post to which his father, long associated with Dr. Barnardo's, had the joy of welcoming him officially. He examined for the Royal College of Surgeons, the Society of Apothecaries, and the University of Cambridge. With all this he was assiduous in his attendance at "the London" and was an inspiring teacher. In 1942 Robert Milne retired and was appointed consultant surgeon. But though ceasing active work at the hospital he was still active in mind and body. He had been civil consultant in orthopaedics to the Royal Navy since 1939, so on his retirement, nothing daunted, he shaved off his moustache and reappeared in the uniform of a surgeon rear-admiral and spent the remainder of the war devoting his considerable talents to the welfare of the Royal Navy.



Robert Milne was a most lovable character. Kindly, good-tempered, approachable, he was the soul of courtesy, and the one thing that moved him to wrath was discourtesy in any form. He had an impish sense of humour and an endearing propensity to kindly leg-pulling. As an orthopaedic surgeon he was conservative, having, one felt, in the course of his wide experience seen almost all the mistakes of over-enthusiasm. But his tidy, accurate, unhurried, and calm technique was an object lesson; his knowledge of the details of almost every form of human labour, which he applied with uncanny judgment to the problems of the partially disabled, was encyclopaedic; his memory for clinical details was astonishing. As a teacher he had the rare gift of imparting judgment as well as facts to his hearers, and his clinics were always packed to overflowing.

Apart from his work and the hospital his one absorbing interest was his family, with perhaps, coming third, an example of his impish humour which his son has described as "a leaning towards the collection of improbable trifles." One suspects that the interests in the byways into which the hunt led him, and in the people that he found there, were the real attraction. "Bobby" Milne's loss is a sore one. He leaves a widow, two sons, and a daughter, to whom the sincerest sympathy of all who knew him will be extended.—O. J. V.-J.

Sir Henry Souttar writes: The loss of Robert Milne will be deeply felt by those who were fortunate enough to be his friends and his colleagues. A quiet unassuming man whose one real interest was in his work and in his patients, he gave devoted service to the hospital which was the centre of his life. His shrewd common sense, not untinged with humour, won the confidence of both his patients and his students, and in every corner of the Commonwealth there are surgeons who owe to Milne their initiation into the correction of deformity. With an obstinacy so characteristic of his countrymen he refused to be divorced from general surgery, but his real affection was for orthopaedics, and in the handling of bones and joints he had a skill and an insight which came from long experience as well as a natural instinct. It was perhaps as an examiner that one saw Milne at his very best, for no one had greater skill in extracting the best from a candidate. He was a good fellow, and many will miss his cheery presence.

H. H. B. writes: Robert Milne, known to most of his friends and colleagues as Bobby, was the son of a deeply loved and respected general practitioner in Bow, an upright man with an unswerving belief in porridge and family prayers and much of the Roman *gravitas* that was so characteristic and, being mellowed by his deep kindliness, so comforting and inspiring a quality in Bobby himself. So far as any man can judge another, Bobby was never ruffled by anything. There was an invisible and infectious serenity in his speech, gait, and all his actions. He published little, but his judgment was seldom, I should imagine, at fault, and personally I never found it so. He was a careful and extremely competent operator and never in a hurry to operate if other measures, in his opinion, could profitably and safely be given a chance. We were friends from the day we first met in the dog-fish and frog-dissecting stage of our education, and if there are not, alas, very many survivors from that period there must be thousands of younger men who will be feeling the loss of one of the kindest and staunchest of companions, teachers, and helpers in every sort of trouble.

Dr. William George Simpson Thomson, who died on September 20 at the age of 62, had been deputy medical superintendent at Cheadle Royal for twenty-seven years. He was educated at Aberdeen, where he graduated first in classics and as M.B., Ch.B. in 1911. He took the D.P.H. in 1914 and the D.P.M. at Manchester in 1925. After a period as house-physician in the Aberdeen Infirmary he was for a time assistant medical officer at the county mental hospital at Cheddleton, Staffordshire, where he had considerable experience in mental disease. He was also a neurologist to the pensions boards set up after the 1914–18 war. In 1922 he was appointed senior assistant medical officer to the Manchester Royal Hospital, Cheadle, and two years later he became deputy medical superintendent. For many years Dr. Thomson was visitor to the licensed houses under the Mental Deficiency Act for the City of Manchester Courts. He was a member of the Royal Medico-Psychological Association and acted as an external examiner for the University of Manchester. He was a good general neurologist, and his advice was often sought on the diagnosis and treatment of functional and organic diseases of the central nervous system.—E. M. B.

Mr. Harry Freeman died on September 29 at a time when he had just attained his ambition of devoting his life to surgery. Born in 1894, he obtained an entrance scholarship in anatomy and physiology at King's College, London. He became a member of the Pharmaceutical Society, and by working as a dispenser in the evenings he earned money to help pay his hospital fees. He had a distinguished career at the Westminster Hospital, where he won the Bird gold medal and prize, the Chadwick prize, and the Sturges prizes for clinical medicine and surgery. He qualified in 1921, and after a resident appointment

as casualty house-surgeon at the Westminster Hospital he went into general practice in Dalston. Freeman's personality and skill soon brought him a large and busy practice, but he found time to keep in contact with hospital work at the Prince of Wales Hospital, Tottenham, where he held a series of clinical assistantships. In 1932 he obtained the diploma of master of midwifery of the Society of Apothecaries, moved to the West End of London, and practised midwifery. Six years later, at the age of 44, he passed the primary examination for the F.R.C.S., and he became a Fellow in 1941. By a stroke of good fortune he was able to perform surgical operations with a senior acting as his "assistant" during the war years. He took every advantage of this opportunity and soon became a competent surgeon. As an associate lecturer on surgery at the North-East London Postgraduate College he helped undergraduates who had failed in surgery at their first examination to pass at their second attempt. During the whole of the war he and his wife were in charge of an air-raid casualty centre in Holborn, and they were both on duty at this centre every night. He also operated on air-raid casualties at the Royal Albert Dock Hospital. Sir Hugh Griffiths has paid tribute to him as a "skilled and kindly surgeon and very gallant gentleman." Harry Freeman was appointed assistant surgeon to the National Temperance and Albert Dock Hospitals in 1946. Subsequently he studied gastroscopy under Mr. Hermon Taylor and published original articles on this subject. He also wrote a section of a book on gastroscopy which is in course of publication. His courage, strength of character, hard work, and great ability, which enabled him to conquer his early difficulties, will remain an inspiration to his friends. He leaves a devoted wife, who is in active medical practice, and two daughters, who are married and live abroad.—W. E. T.

Dr. DONALD CAMPBELL died on June 19 at his home near St. Helens, Lancs, at the age of 66. Dr. Campbell qualified in Dublin in 1915. He had been in general practice in St. Helens since 1919, and his sudden death came as a shock to his colleagues, since he had been working right up to the last. In 1928, while still in practice, he took the M.R.C.P. During the 1914–18 war Dr. Campbell served first of all as a combatant in the Indian Army and was later transferred to the R.A.M.C., serving in France, where he was wounded. During the recent war he was a medical officer for the local Home Guard. Dr. Campbell had studied in the School of Medical History at Oxford, and he was the author of *Arabian Medicine and its Influence in the Middle Ages*. He had always been interested in medico-political work and was honorary secretary of the local panel committee from 1924 onwards. He was chairman of the St. Helens Insurance Committee from 1933 until 1948, when he became vice-chairman of the local executive council. Dr. Campbell was always a helpful and agreeable colleague, and he will be sadly missed by his patients and his friends in the St. Helens area.—A. A. W. M.

Dr. JANET YOUNG LAIDLAW died on August 9 at the age of 66 after a long illness. She was a student at the London School of Medicine for Women, and qualified in 1931. She graduated M.B., B.S. two years later, and was for a time a resident house-physician at the Royal Free Hospital. Thereafter her professional work was mainly among children. She was school medical officer in Cambridge until increasing ill-health enforced her retirement just over a year before her death.

K. F. writes: I first knew Janet Laidlaw when we were students together over 20 years ago. She was then in her late thirties, for her opportunity to study medicine had only just arrived. Her determination and tenacity were almost hidden by her quiet and unobtrusive manner. She did not seek knowledge, or skill, or advancement for her own ends, but because she cared about the needs and the rights of others. Humility, integrity, charity—those of us who knew her and loved her know that she measured up to the true meaning of these old-fashioned words. Outside her work among the children whom she loved and understood her interests were in her own folk, in her garden, and in the little house in Galloway to which she turned whenever she could and which she had made into a haven of rest and peace for her friends.

Medico-Legal

DOCTOR CENSURED

TRIBUNAL FINDINGS

A Tribunal set up under Section 42 of the National Health Service Act recently considered a case which was reported in these columns (June 4, p. 1009) when it came before the Medical Services Committee of the West Sussex Executive Council. At the hearing both the complainant and the respondent medical practitioner were legally represented.

The Tribunal found as facts that the doctor, when he attended the infant whose father made the original complaint, "was under the influence of alcohol to such an extent that his professional judgment was impaired"; and that on the night in question the doctor had failed to notify his partner of his intention to be away. Though the respondent might have arrived at the house with greater promptitude than he did, it could not be said that the delay in his arrival was unreasonable or excessive. The doctor then examined the child, failed to appreciate that it was gravely ill, failed to prescribe any treatment for it, and left the house about 10 minutes after he had arrived. Within the next half-hour the child died. The doctor admitted before the Tribunal a serious error of professional judgment, an error which might well not have been made had he not been under the influence of alcohol.

The Tribunal did not find that the doctor failed to make a proper examination of the infant. Nevertheless all the members of the Tribunal took "an extremely grave and serious view of the conduct and behaviour of the doctor" on the night in question. However, the Tribunal considered that all these facts amounted only to a single incident and came to the conclusion that it was not justified in saying that this single incident was such as to cause the inclusion of the respondent in the Medical List to be prejudicial to the efficiency of the General Medical Services. The Tribunal was further of the opinion that "in all probability no treatment, whatever it might have been, would if administered at the time at which the respondent arrived at the house (or possibly even three or four hours earlier) have saved the life of the child" and that "no negligence of the respondent in any way caused or contributed to the death of the child."

The Tribunal made no order as to the costs of the parties to the inquiry.

Universities and Colleges

UNIVERSITY OF CAMBRIDGE

Thomas Shirley Hele, M.D., F.R.C.P., Master of Emmanuel College, has been reappointed a Deputy Vice-chancellor of the University for the year 1949–50.

UNIVERSITY OF LONDON

A course of six lectures in physiology will be delivered by Dr. Bernhard Katz at University College, Gower Street, London, W.C., on Fridays, October 21 and 28 and November 4, 11, 18, and 25, at 5.15 p.m. His subject is "Transmission of Excitation in Nerve and Muscle."

Dr. Charity Waymouth will deliver two lectures on "Technique and Applications of Tissue Culture" at University College on Mondays, October 24 and 31, at 4.45 p.m.

A course of four lectures on "Bacterial Toxins" will be delivered by Dr. W. E. Van Heyningen at University College on Mondays, November 7, 14, 21, and 28, at 4.45 p.m.

On Monday, December 5, at 5.30 p.m., Dr. G. L. Brown, Jodrell Professor of Physiology in the University, will deliver his inaugural lecture at University College.

Professor V. du Vigneaud, of Cornell University Medical College, will deliver a course of three lectures on "The Indispensability of Biologically Labile Methyl Groups in the Diet and Transmethylation" in the Meyerstein Lecture Theatre, Westminster Medical School, Horseferry Road, London, S.W., on October 28 and 31 and November 2, at 5.30 p.m.

Admission to all the above lectures is free, without ticket.

INFECTIOUS DISEASES AND VITAL STATISTICS

We print below a summary of Infectious Diseases and Vital Statistics in the British Isles during the week ended September 24. [No. 38

Figures of Principal Notifiable Diseases for the week and those for the corresponding week last year, for: (a) England and Wales (London included). (b) London (administrative county). (c) Scotland. (d) Eire. (e) Northern Ireland.

Figures of Births and Deaths, and of Deaths recorded under each Infectious disease, are for: (a) The 126 great towns in England and Wales (including London). (b) London (administrative county). (c) The 16 principal towns in Scotland. (d) The 13 principal towns in Eire. (e) The 10 principal towns in Northern Ireland.

A dash — denotes no cases; a blank space denotes disease not notifiable or no return available.

Disease	1949					1948 (Corresponding Week)				
	(a)	(b)	(c)	(d)	(e)	(a)	(b)	(c)	(d)	(e)
Cerebrospinal fever	35	4	17	1	1	26	2	12	2	1
Deaths		1	—				—	1		
Diphtheria	92	13	34	5	2	125	12	38	6	1
Deaths	2	—	—	—	1	1	—	—	—	—
Dysentery	78	16	76	—	—	68	22	49	1	—
Deaths				—	—				—	—
Encephalitis lethargica, acute	4	—	—	—	—	1	—	—	—	—
Deaths		—					1			
Erysipelas			30	9	2			30	11	—
Deaths		—					—			
Infective enteritis or diarrhoea under 2 years				136					29	
Deaths	30	4	7	8	5	22	1	14	3	—
Measles*	659	50	18	25	30	2,703	91	60	11	37
Deaths†			—	—	—			—	—	1
Ophthalmia neonatorum	44	2	10	—	—	36	2	11	—	2
Deaths										
Paratyphoid fever	23	2	2 (B)	7 (B)	1 (B)	15	1	—	1 (B)	—
Deaths	1	—	—	—	—	—	—	—	—	—
Pneumonia, influenzal	226	10	1	1	3	277	12	1	1	3
Deaths (from influenza)‡	5	1	—	—	—	7	—	—	1	—
Pneumonia, primary			118	8				117	10	
Deaths	113	18		6	6	120	17		2	6
Polio-encephalitis, acute	27	6				3	—			
Deaths										
Poliomyelitis, acute	268	42	7	3	1	70	2	3	—	—
Deaths§	12	1				4	—			
Puerperal fever		—	6				—	16		—
Deaths										
Puerperal pyrexia‖	88	5	5	—	1	87	8	2	—	—
Deaths		—					—			
Relapsing fever	—	—			—	—	—			—
Deaths										
Scarlet fever	1,097	78	165	73	95	1,068	70	216	130	38
Deaths†			—	1	—			—	—	—
Smallpox	—	—	—	—	—	—	—	—	—	—
Deaths				—	—				—	—
Typhoid fever	8	3	1	5	1	29	—	1	3	—
Deaths	—	—	—	1	—	—	—	—	—	—
Typhus fever	—	—	—	—	—	—	—	—	—	—
Deaths				—	—				—	—
Whooping-cough*	1,061	39	47	43	34	2,259	170	64	48	8
Deaths	2	—	—	1	—	8	1	1	2	—
Deaths (0–1 year)	213	25	33	20	11	250	30	53	13	12
Deaths (excluding stillbirths)	3,895	596	524	144	108	4,008	651	556	149	106
Annual death rate (per 1,000 persons living)			10·5	8·9				11·2	9·3	
Live births	7,111	1061	800	382	244	7,458	1166	885	463	223
Annual rate per 1,000 persons living			16·0	23·7				17·9	29·0	
Stillbirths	187	30	23			169	17	23		
Rate per 1,000 total births (including stillborn)			28					25		

* Measles and whooping-cough are not notifiable in Scotland, and the returns are therefore an approximation only.

† Deaths from measles and scarlet fever for England and Wales, London (administrative county), will no longer be published.

‡ Includes primary form for England and Wales, London (administrative county), and Northern Ireland.

§ The number of deaths from poliomyelitis and polio-encephalitis for England and Wales, London (administrative county), are combined.

‖ Includes puerperal fever for England and Wales and Eire.

EPIDEMIOLOGICAL NOTES

Poliomyelitis

The total number of notifications in England and Wales in the week ended October 1 was: poliomyelitis 331 (268), polio-encephalitis 26 (27). The figures for the previous week are shown in parentheses. These are the highest figures this year. In 1947 figures for the corresponding week were poliomyelitis 441, polio-encephalitis 32.

Multiple cases (poliomyelitis and polio-encephalitis together) were reported from the following counties: London 44 (48), Bedford 5 (1), Berkshire 5 (3), Buckingham 2 (1), Chester 4 (7), Cornwall 8 (8), Dorset 5 (4), Durham 3 (1), Essex 26 (17), Gloucester 17 (0), Hertford 12 (7), Kent 19 (18), Lancaster 41 (24), Leicester 2 (5), Norfolk 4 (2), Northampton 4 (4), Northumberland 6 (13), Nottingham 9 (9), Somerset 6 (7), Southampton 7 (8), East Suffolk 2 (5), Surrey 9 (11), East Sussex 5 (1), Warwick 13 (8), Wiltshire 8 (9), East Yorks 3 (1), North Yorks 2 (1), West Yorks 38 (19), Glamorgan 6 (3), Monmouth 2 (0).

Discussion of Table

In *England and Wales* decreases were recorded in the notifications of whooping-cough 119 and acute poliomyelitis 43. There were increases in the incidence of scarlet fever 155 and diphtheria 14.

The local trends of scarlet fever showed only small variations from the preceding week except in Yorkshire West Riding, where there was an increase of 55. Notifications of diphtheria have almost been doubled in the past month; the chief feature of the returns was a rise of 17 in Lancashire (14 of the 26 cases in this county were notified in Liverpool C.B.).

There were only small variations in the local trends of measles, the largest being an increase of 27 in Lancashire. The largest fluctuations in the notifications of whooping-cough were decreases in Middlesex 29 and Essex 30.

In Durham, Hetton U.D., where 15 cases were reported in the preceding week, 17 further cases of dysentery were notified. Other large returns for dysentery were London 16, Lancashire 16 (Liverpool C.B. 10), Glamorganshire 8 (Cardiff C.B. 6). Outbreaks of food-poisoning were notified in Yorkshire West Riding 55 (Batley M.B. 32, Sheffield C.B. 20); Essex 59 (Southend-on-Sea C.B. 19); and London 34.

In *Scotland* there were increases in the notifications of scarlet fever 33, acute primary pneumonia 33, and dysentery 22, with decreases in the incidence of whooping-cough 28 and measles 22. The rise in the notifications of scarlet fever occurred in the western area. Of the 76 cases of dysentery 60 were notified in Glasgow.

In *Eire* the notifications of measles were 23 fewer than in the preceding week, while increases were reported for scarlet fever 11 and whooping-cough 10. The incidence of diarrhoea and enteritis remained high at 136 for the whole country; of these, 101 were notified in Dublin C.B. The rise in the notifications of scarlet fever and whooping-cough was contributed by Dublin C.B.

In *Northern Ireland* decreases were reported in the notifications of measles 10 and whooping-cough 11. The incidence of scarlet fever remained at the high level of the preceding week.

Week Ending October 1

Notifications of infectious diseases in England and Wales during the week included: scarlet fever 1,305, whooping-cough 956, diphtheria 76, measles 780, acute pneumonia 313, cerebrospinal fever 25, acute poliomyelitis 331, acute polio-encephalitis 26, dysentery 163, paratyphoid fever 24, typhoid fever 12, food-poisoning 553.

The council of Dr. Barnardo's Homes announces that the Watts Naval Training School at Elmham, Norfolk, and the Russell-Cotes Nautical School at Parkstone, Dorset, are to be amalgamated as one establishment under the new title of the Parkstone Sea Training School. As a consequence of this change the Watts School will cease to function as a sea-training centre and will for the time being become a branch home for boys.

Medical News

Appointments to Royal Households

Dr. J. N. Loring has been appointed Apothecary to His Majesty's Medical Household in the room of Sir Frederick Stanley Hewett, who has been appointed Extra Surgeon Apothecary to His Majesty's and to Queen Mary's Medical Households. Dr. Loring has also been appointed Apothecary to Queen Mary's Medical Household and to the Household of Princess Elizabeth and the Duke of Edinburgh. Sir James Walton has been appointed an Extra Surgeon and Mr. Guy Capper Birt an Extra Surgeon Dentist to Her Majesty Queen Mary's Medical Household. All the appointments date from October 1.

Unesco Book Coupons

Individuals and institutions in "soft currency" countries may obtain book coupons to facilitate buying books or periodicals from the U.S.A., Switzerland, Czechoslovakia, India, and France. The coupons have a dollar face value, and may be bought with sterling from Unesco Book Coupons, Book Tokens Limited, 28, Little Russell Street, London, W.C.1. Further particulars may be obtained from the same address.

Gold Medal

The South Wales Institute of Engineers has awarded Dr. T. H. Jenkins the Institute Gold Medal for 1948 for his paper "Medico-mining Aspects of Pneumoconiosis in South Wales." Dr. Jenkins is divisional medical officer for the South-Western Division of the National Coal Board. While working as a collier in the Garw Valley he matriculated in 1924 and entered the University College of South Wales. He obtained his B.Sc. in mining, and subsequently studied medicine at University College Hospital, London, where he took the conjoint diploma and London degree in 1938.

Sir Sydney Smith

The honorary degree of M.D. of the University of Louvain was conferred upon Sir Sydney Smith, Regius Professor of Forensic Medicine and Dean of the Faculty of Medicine in the University of Edinburgh, at Louvain on October 10.

A New Journal

The Institute of Laryngology and Otology, Royal National Throat, Nose and Ear Hospital, has commenced publication of a new journal, *Annals of the Institute of Laryngology and Otology*. The *Annals* will publish reports of the work of the hospital, and contributions are invited from past and present members of the Institute. Based as they are on the largest hospital in Britain devoted solely to otorhinolaryngology, the *Annals* are an important addition to medical literature. They will appear half-yearly, price 5s. per issue, and are published from 330, Gray's Inn Road, London, W.C.1.

The American Heart Association's Journal

The American Heart Association is to begin publishing in January a new official monthly journal entitled *Circulation—The Journal of the American Heart Association*. With the new publication the American Heart Association will terminate sponsorship of the monthly *American Heart Journal* with the December, 1949, number. According to the announcement issued by the American Heart Association, "The needs of the members of the American Heart Association and of the medical profession in general require a larger official journal to keep pace with advances in the field of cardiovascular diseases. *Circulation* will be published in a larger format . . . which will assure accelerated publication of articles, bringing valuable medical material to the professional reader at the earliest possible opportunity." Dr. Thomas M. McMillan, for some years editor-in-chief of the *American Heart Journal*, will continue in that capacity for *Circulation*, and it is expected that the associate editors and editorial board of the older publication will also serve in the same capacities on the new magazine. The publishers will be Grune and Stratton, Inc., 381, Fourth Avenue, New York, 16.

Invested with G.C.V.O.

The King invested Sir Maurice Cassidy with the insignia of the G.C.V.O. at his home on October 10. Sir Maurice Cassidy was unable to go to Buckingham Palace to receive the honour, which, as reported previously, was gazetted in May, because of the injuries that he received in a car accident six months ago.

Photographic Exhibition

The Royal Photographic Society's annual exhibition at 16, Princes Gate, London, S.W.7, includes a number of photographs of interest to medical men. The illustrations of the pathological specimens of heart and kidney showed the remarkable clarity that photography can attain in skilled hands. Much depends on adept lighting of the object, as was shown particularly clearly in five photographs of a man with exophthalmic ophthalmoplegia directing his eyes to show the effects of the disorder. These photographs are of a quality that deserves study by anyone wanting to illustrate an article or a textbook. The exhibition remains open until October 26.

Periodicals at Special Rates

The Times has announced that full-time students may now buy it for 2d. Inquirers should write to the Manager, Subscription Department, *The Times*, Printing House Square, London, E.C.4. The weekly journal, the *Spectator*, is now obtainable by members of the medical profession for the special subscription of £1 1s. instead of 30s. a year. Particulars may be obtained from the *Spectator*, 99, Gower Street, London, W.C.1.

Tuberculosis as Industrial Disease

The Industrial Diseases Subcommittee of the Industrial Injuries Advisory Council is considering whether tuberculosis should be a "prescribed disease" under the National Insurance (Industrial Injuries) Act for nurses and other classes of health workers. "Prescribing" a disease in relation to any particular class of person makes the benefits provided under the Industrial Injuries Act available to people in that class if they are employed under a contract of service and develop the disease as a result of their employment. Industrial injury benefits are appreciably greater than those obtained under the National Insurance Act. Persons and organizations are invited to submit written evidence as soon as possible, and in any case before December 1, to Mr. F. K. Forrester, Ministry of National Insurance, 6, Curzon Street, London, W.1, who will supply further information on request.

B.C.G. from Denmark

The first consignment of B.C.G. to be imported under the Ministry of Health's scheme arrived in England by air from Copenhagen on October 3, and was sent to the Public Health Laboratory at Colindale. Part of the consignment, which contained 30 ml. of the vaccine, is to be used at the Children's Hospital at Sheffield, where some of the staff have volunteered to be vaccinated. The arrangements for trying out B.C.G. in this country were described in the *Journal* of July 2 (p. 29).

Child Health Lectures in Czechoslovakia

Professor J. C. Spence, Professor of Child Health in the University of Durham, is now in Czechoslovakia lecturing for the British Council. The Czech Ministry of Health, the Czech Paediatric Society, the Czechoslovak-British Medical Society, and the Institute of Social Medicine, Charles University, have co-operated in arranging the tour.

Wills

Dr. Alan Leonard Smith Tuke, of Dunfermline, left £65,246; Dr. George Ezra Halstead, of Bideford, £22,394; Dr. Alexander McConnell Erskine, of Goole, £18,477; and Dr. Percy Kitchin, formerly of Bournemouth, £46,847.

COMING EVENTS

Royal Medical Society

The 1949–50 session of the Royal Medical Society of Edinburgh (7, Melbourne Place, Edinburgh) opens to-day (Friday, October 14) at 8 p.m., when Professor A. Murray Drennan delivers the inaugural address entitled "Whither Are We Going?" Further meetings will be held on Fridays at 8 p.m., as follows: October 21, Mr. K. Wood, "Clubbing of the Fingers"; October 28, Sir Philip Manson-Bahr, "The Dawn of Tropical Medicine (The Life and Work of Sir Patrick Manson)"; November 4, Mr. C. W. Mercer, "The Aetiology and Treatment of Ulcerative Colitis"; November 11, Mr. R. C. Tyldesley, "Unorthodox Healing—An Assessment"; November 25, Mr. A. H. Duncan, "The Aetiology of Neoplasia"; December 2, Mr. J. J. MacCabe, "Disseminated Sclerosis"; December 9, symposium on "Pyrexia"; January 13, dissertation by Mr. I. B. Tait; January 20, Mr. D. W. MacLean, "The Handicapped Child"; January 27, Sir Hugh Cairns, "Head Injuries"; February 3, Mr. J. B. McWhinnie, "Physique, Diathesis, and Temperament"; February 10, dissertation by Mr. L. R. Roberts; February 17, Professor Walter Mercer, "Manipulative Surgery"; February 24, Mr. A. Fraser Darling, "The Nature of Cutaneous Sensation"; March 3, Sir Edward Mellanby, F.R.S., "Widespread Nerve Degeneration due to Abnormal Bone Growth—An Experimental Investigation"; March 10, valedictory address by the senior president. The presidents' annual dinner will be held at the Royal College of Physicians of Edinburgh, Queen Street, Edinburgh, on Thursday, November 17, at 7.15 for 7.30 p.m., when Sir Alexander Fleming, F.R.S., will be the guest of honour. The annual extraordinary general meeting of the society will be held on Wednesday, March 15, at 7 p.m.

Hunterian Society

The programme of the Hunterian Society for the 1949–50 session is as follows: October 17, 7 for 7.30 p.m., dinner-meeting at Talbot Restaurant, 64, London Wall, E.C., presidential address by Dr. William Thomson Brown on "Balance"; November 21, 8.30 p.m., at Society of Apothecaries of London, Black Friars Lane, Queen Victoria Street, E.C., discussion, "That Alcohol has Contributed more to the Happiness than to the Misery of Mankind," proposed by Dr. John Y. Dent and Dr. Desmond Curran and opposed by Dr. Henry Yellowlees and Mr. Archibald Crawford, K.C.; December 5, 7 for 7.30 p.m., dinner-meeting at Talbot Restaurant, discussion, "The Assessment of Surgical Risk," to be opened by Sir Horace Evans, Dr. Frankis T. Evans, and Mr. A. Lawrence Abel; January 16, 8.30 p.m., at Mansion House, London, E.C., Hunterian Lecture by Professor René-A. Gutmann (Paris), "The Early Diagnosis of Gastric Carcinoma"; February 16, at Grosvenor House, Park Lane, London, W., annual dinner; February 27, 8.30 p.m., at Mansion House, Hunterian Oration by Dr. Daniel T. Davies, "John Hunter, the Man and his Message"; March 20, 7 for 7.30 p.m., dinner-meeting at Talbot Restaurant, discussion, "Modern Trends in the Diagnosis and Treatment of Pulmonary Tuberculosis," to be opened by Dr. Geoffrey Marshall and Mr. T. Holmes Sellors; April 17, 7 for 7.30 p.m., annual general dinner-meeting at Talbot Restaurant, followed by a demonstration of hypnotism by Mr. Peter Casson.

Edinburgh Lectures

In connexion with the postgraduate courses in medicine and surgery the Edinburgh Postgraduate Board for Medicine has arranged a series of open lectures on subjects of wide biological interest to be given on Tuesdays, at 5 p.m., during the winter term in the Anatomy Lecture Theatre, Edinburgh University New Buildings, beginning on October 25. All students and graduates are invited to attend. Details will be published under "Societies and Lectures" in the *Journal*.

Forensic Medicine Congress

The Third Congress of the International Academy of Forensic and Social Medicine will be held in Cairo on March 21–26, 1950.

Institute of Diseases of the Chest

A ceremony to mark the opening of the new premises of the Institute of Diseases of the Chest (British Postgraduate Medical Federation) in the grounds of Brompton Hospital, Fulham Road, London, S.W., will be held on Wednesday, October 26, at 3 p.m., when inaugural addresses will be delivered by Sir John Anderson, chairman of the Governing Body of the Federation, Sir Francis Fraser, director of the Federation, Sir Robert A. Young, chairman of the Board of Governors of the Hospitals for Diseases of the Chest and consulting physician to Brompton Hospital, and Dr. S. Roodhouse Gloyne, consulting pathologist to the London Chest Hospital.

London Hospital Old Students' Dinner

The London Hospital Old Students' Dinner will be held at the Trocadero Restaurant, Piccadilly Circus, London, W., on Thursday, October 27. Tickets, price £1 1s., can be obtained from Dr. R. R. Bomford, 6, Devonshire Place, London, W.1.

SOCIETIES AND LECTURES

Friday

Royal Medical Society, 7, Melbourne Place, Edinburgh.—October 14, 8 p.m., *"Whither Are We Going?"* Inaugural address by Professor A. Murray Drennan.

Monday

Hunterian Society.—At Talbot Restaurant, 64, London Wall, E.C., October 17, 7 for 7.30 p.m., dinner-meeting; *"Balance,"* Presidential address by Dr. William Thomson Brown.

Institute of Laryngology and Otology, 330–332, Gray's Inn Road, London, W.C.—October 17, 2.30 p.m., *"Tumours of the Post-nasal Space,"* by Mr. F. C. W. Capps.

London University.—At University College, Gower Street, London, W.C., October 17, 5.15 p.m., *"The Structure of Peripheral Nerve,"* by Professor J. Z. Young.

Tuesday

Institute of Laryngology and Otology, 330–332, Gray's Inn Road, London, W.C.—October 18, 2.30 p.m., *"Malignant Diseases and Radiotherapy,"* by Mr. W. A. Mill.

Royal College of Physicians of London, Pall Mall East, S.W.—October 18, 3 p.m., *"Individuality in Medicine,"* Harveian Oration by Dr. Geoffrey Marshall.

Society for the Study of Addiction.—At Medical Society of London, 11, Chandos Street, Cavendish Square, W., October 18, 4 p.m., *"The Problems for Research in the Study of Addiction,"* Presidential address by Professor F. L. Golla. A discussion will follow.

Wednesday

Glasgow University: Department of Ophthalmology.—October 19, 8 p.m., *"Tobacco Amblyopia,"* by Dr. R. Leishman.

Harveian Society of London.—At King's College Hospital Medical School, Denmark Hill, S.E., October 19, 4.15 p.m., Clinical meeting.

London University.—At University College (Anatomy Theatre), Gower Street, W.C., October 19, 5.30 p.m., *"Growth and Reproduction of Bacteria,"* by Sir Paul Fildes, F.R.S.

North-East Metropolitan Regional Tuberculosis Society.—October 19, 2.30 p.m., visit to Ware Park Sanatorium, Herts. *"Resection of the Lung for Pulmonary Tuberculosis,"* by Mr. O. S. Tubbs.

Royal Institute of Public Health and Hygiene, 28, Portland Place, London, W.—October 19, 3.30 p.m., *"The Present Position of Diphtheria Immunization,"* by Dr. W. W. King-Brown.

Society of Radiographers.—At Royal College of Nursing (Cowdray Hall), 1A, Henrietta Place, Cavendish Square, London, W., October 19, 6.30 p.m., *"The Radiography of Infants and Children,"* Stanley Melville Memorial Lecture by Dr. C. G. Teall.

Thursday

British Institute of Radiology, 32, Welbeck Street, London, W.—October 20, 8.15 p.m., discussion: *"Instrumental Aids to Diagnostic Techniques."* Speakers: Dr. T. H. Hills, Mr. R. W. Stanford, Dr. G. R. Airth, and Mr. E. D. Ormerod.

Edinburgh Clinical Club.—In B.M.A. Rooms, 7, Drumsheugh Gardens, Edinburgh, October 20, 8 p.m., opening meeting of club, *"Discussion on the Problems of Married Life,"* by Reverend W. S. Tindal and Dr. W. P. Kraemer.

Institute of Urology.—At Royal College of Surgeons of England, Lincoln's Inn Fields, London, W.C., October 20, 5 p.m., *"The Conservative Treatment of Hydronephrosis,"* by Professor V. W. Dix.

London University.—At University College (Anatomy Theatre), Gower Street, W.C., October 20, 5.30 p.m., *"Growth and Reproduction of Bacteria,"* by Sir Paul Fildes, F.R.S.

Royal Society of Tropical Medicine and Hygiene, 26, Portland Place, London, W.—October 20, 7.30 p.m., *"Tropical Medicine as a Career,"* Presidential address by Professor H. E. Shortt.

St. George's Hospital Medical School, Hyde Park Corner, London, S.W.—October 20, 4.30 p.m., lecture-demonstration: *"Neurology,"* by Dr. D. J. Williams.

Friday

FACULTY OF RADIOLOGISTS.—At Royal College of Surgeons of England, Lincoln's Inn Fields, London, W.C., October 21, 2.15 p.m., Diagnosis Section meeting, *"The Value of Tannic Acid Barium Enema in Colonic Investigation,"* by Dr. J. H. L. Conway-Hughes; *"The Causes of Failure After Gastrectomy for Peptic Ulcer,"* by Dr. C. N. Pulvertaft; *"The X-ray Appearances of Acquired Collapse (Atelectasis) of the Upper Lobes,"* by Dr. G. Simon.

INSTITUTE OF PHYSICS: INDUSTRIAL SPECTROSCOPY GROUP.—At 47, Belgrave Square, London, S.W., October 21, 4 p.m., annual general meeting; *"Physical Methods in the Forensic Laboratory,"* by Dr. F. G. Tryhorn.

LONDON UNIVERSITY.—At University College, Gower Street, London, W.C., October 21, 5.15 p.m., *"Transmission of Excitation in Nerve and Muscle,"* by Dr. Bernhard Katz.

LONDON UNIVERSITY.—At University College (Anatomy Theatre), Gower Street, W.C., October 21, 5.30 p.m., *"Growth and Reproduction of Bacteria,"* by Sir Paul Fildes, F.R.S.

ROYAL INSTITUTE OF PHILOSOPHY, 14, Gordon Square, London, W.C. —October 21, 5.15 p.m., *"Russell's Theory of the External World,"* by Professor H. H. Price.

ROYAL MEDICAL SOCIETY, 7, Melbourne Place, Edinburgh.—October 21, 8 p.m., *"Clubbing of the Fingers,"* by Mr. K. Wood.

WEST LONDON MEDICO-CHIRURGICAL SOCIETY.—At South Kensington Hotel, 41, Queen's Gate Terrace, London, S.W., October 21, 7.15 p.m. for 7.30 p.m., dinner; 8.30 p.m., *"The Dramatic in Gynaecology and Obstetrics,"* Presidential address by Mr. V. B. Green-Armytage.

Saturday

BIOCHEMICAL SOCIETY.—At Biochemistry Department, King's College, Strand, London, W.C., October 22, 2 p.m., 280th meeting.

APPOINTMENTS

Dr. Herbert Kent, formerly Fellow in Physical Medicine and Rehabilitation of the New York University, Bellevue Medical Center, and National Foundation for Infantile Paralysis, has been appointed Chief of Physical Medicine Rehabilitation at the Veterans Administration Hospital, Indianapolis.

The Secretary of State for Scotland has appointed Dr. Catherine Haldane Stobie Begg to be a Deputy Commissioner of the General Board of Control for Scotland.

Dr. Begg graduated M.B., Ch.B. at Glasgow University in 1932 and has held appointments in Glasgow Royal and Western Infirmaries, Glasgow Southern General Hospital, and various mental hospitals. She is at present Senior Medical Officer at Stoneyetts Mental Hospital, Glasgow.

CENTRAL COUNCIL FOR HEALTH EDUCATION.—The following appointments have been announced: *Deputy to the Medical Adviser and Secretary*, L. J. H. Burton, M.R.C.S., L.R.C.P., D.P.H.; *Assistant*, Anne F. Burgess, M.B., Ch.B. L.D.S.

NELSON, IVAN D. M., M.B., Ch.B., D.P.H., Deputy Medical Officer of Health, County Borough of Dewsbury.

RAFTERY, LILIAN, M.R.C.S., L.R.C.P., M.M.S.A., M.R.C.O.G., Assistant Visiting Gynaecologist and Obstetrician, King Edward VIII Hospital, Durban, South Africa.

RUNWELL HOSPITAL, near Wickford, Essex.—*Clinical Research Fellow*, P. Macdonald Tow, M.B., B.S. *Senior Registrar*, M. G. Valentine, M.D., D.P.M.

STEWART, R. H. M., M.D., Assistant Senior Medical Officer, Manchester Regional Hospital Board.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Black.—On October 2, 1949, at Dunfermline, to Hilda (née Murray), wife of J. Murray Black, F.R.C.S.Ed., a daughter.

Ferguson.—On September 6, 1949, at Douglas, Isle of Man, to Frances (née Wright), wife of Dr. J. H. Ferguson, a brother for Frances, Elizabeth, and Robert—George Wright.

Mills.—On October 6, 1949, to Margaret Jane, M.B., D.A., wife of Wilfrid Mills, F.R.C.S., a son.

MARRIAGES

Binns—Whitaker.—On September 17, 1949, at Ewell, Surrey, Surgeon Lieutenant-Commander George Augustus Binns, R.N., of Leicester, to Joan Whitaker, of Ewell.

DEATHS

Aspinwall.—On October 2, 1949, at Heswall, Cheshire, Joan Fullerton Aspinwall, M.R.C.S., L.R.C.P., aged 85.

Bentley.—On September 26, 1949, Harold Bentley, M.R.C.S., L.R.C.P., late of Mitcham, Surrey.

Ford.—On October 3, 1949, at 2, Derwent Road, Eastbourne, Frank Chubb Ford, M.R.C.S., L.R.C.P., late of Wimbledon and Rotherfield, aged 82.

Freeman.—On September 29, 1949, Harry Freeman, F.R.C.S., M.M.S.A., of 69, Harley House, London, N.W.

Greenwood.—On October 5, 1949, in London, Major Greenwood, D.Sc., F.R.C.P., F.R.S., of Hillcrest, 102, Church Hill, Loughton, Essex, aged 69.

Hoffman.—On September 26, 1949, at his home, The Red House, Cranham, Gloucester, Geoffrey Arthur Hoffman, B.A., M.B., T.C.Dub.

Johns.—On September 27, 1949, at the Old Mill House, Adderbury, Oxon, Archibald Tisdall Johns, M.D., aged 77.

Mathews.—On September 24, 1949, at Wayside, Gossamer Lane, Aldwick, Bognor Regis, Sussex, William L'Estrange Mathews, M.R.C.S., L.R.C.P.

Prentice.—On September 19, 1949, in hospital, John Stuart Prentice, M.B., Ch.B.

Williams.—On September 21, 1949, Geoffrey Commeline Williams, O.B.E., M.R.C.S., L.R.C.P., D.P.H., of 8, Belbroughton Road, Oxford.

Any Questions ?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

Trachoma

Q.—*What is the cause of trachoma? How useful are the sulphonamides and antibiotics in the treatment of this condition? Where are the best articles to be found concerning the disease in all its aspects?*

A.—It is now generally agreed that trachoma is due to a virus infection, the virus being one of the large-sized variety. The mode of transmission—for example, the question whether the virus is louse-borne—is still in dispute. As with the other infections due to large-size viruses, the sulphonamides have proved of great value. The place of penicillin in the treatment of trachoma is still uncertain. When the sulphonamides are used it is advisable to eradicate secondary infection by a course of sulphonamide systemically. The trachoma itself appears to be readily amenable to local sulphonamide therapy, which may have to be continued for several months. Daily painting with 30% sodium sulphacetamide, and the use of an ointment of 6% of the same drug three or four times a day, give good results. It is advisable to eradicate as much of the infective material as possible by mechanical means such as expression before starting on local therapy. In old-standing cases eradicating a virus infection does not, of course, overcome mechanical distortion of the lid from shrinkage of tissue.

The best account of modern teaching is the *Aetiology of Trachoma* by L. A. Julianelle (Oxford University Press, 1938). *Trachoma*, by A. F. MacCallan (London, Butterworth & Co., 1936), is also useful, especially for the older teaching. An account of the use of sulphonamides in trachoma is contained in a paper on the treatment of trachoma by Arnold Sorsby in the *British Journal of Ophthalmology* (1945, **29**, 98).

Hyoscine for Sea-sickness

Q.—*A family consisting of the parents and two children, aged 4 and 2, are travelling to South Africa. What would be the appropriate dose of hyoscine in each case? Should it be started before embarkation? How long should it be continued, and are there any side-effects?*

A.—Presumably the hyoscine is intended to prevent sea-sickness. If so, an adult should take a daily dose of 1/100 gr. (0.65 mg.) of hyoscine hydrobromide. One dose daily is enough, taken in the morning. A child of 4 should take one-fifth of this dose, and a child of 2 one-tenth. There is no need to start taking the drug before embarkation. It can be continued throughout the voyage. The only reaction is some dryness of the mouth.

Prostatectomy and Sexual Potency

Q.—*What is now considered the most satisfactory surgical approach in prostatectomy? What is the effect of the operation on the sexual life of an otherwise healthy male of middle age, particularly in relation to potency and libido, power of erection, emission and ejaculation, orgasm, spermatogenesis, and ability to procreate?*

A.—Potency and libido are not usually affected by prostatectomy in a healthy middle-aged male. Many of the patients undergoing prostatectomy have already ceased to have coitus, but Thomson-Walker found that, among males of all ages, no difference was observed in sexual power in 67%; 20% suffered subsequently from a gradual loss of vigour; and 13% became impotent. Ejaculation does not usually occur after enucleation of the prostate, the semen passing back into the bladder and being voided in the next specimen of urine. In spite of this the patient has an orgasm. It is usually said that sterility follows prostatectomy, but the writer has known two or three

cases in which the wife has conceived after her husband has been subjected to prostatectomy. If it were not for the fact that the wives of most men undergoing prostatectomy are themselves past child-bearing age, such cases would probably be more numerous. It must be remembered, however, that many surgeons divide the vasa in order to reduce the incidence of post-operative epididymitis, and that this leads to sterility.

It cannot be said that any one technique of prostatectomy is recognized as being superior to all others. What form of operation is carried out will depend on the state of the patient and on the surgeon's personal opinion. Retropubic prostatectomy and the Harris technique are both excellent operations for certain patients, but they should not be used as routine measures.

Coronary Thrombosis and Air Travel

Q.—*Are there any objections to air travel for patients with a history of coronary thrombosis some years ago?*

A.—Provided oxygen is used for flight above 10,000 feet (3,000 metres) there should be no greater risk to a subject well recovered from a coronary thrombosis in this mode of travel than in any other, and fatigue is likely to be considerably less.

Thrombophlebitis Migrans

Q.—*What is the treatment for repeated attacks of thrombophlebitis over a period of 18 months involving the superficial veins of arms and legs in a woman of 48? The erythrocyte sedimentation rate is 11 mm. in one hour, and the blood pressure 146/90 mm. Hg. She has no infected teeth or gall-bladder infection. Section of an infected vein has shown well-organized thrombus. Sulphonamides, large doses of vitamins, and the usual treatment for phlebitis have been unsuccessful. What further treatment could be tried, and what is the prognosis?*

A.—This patient seems to be suffering from thrombophlebitis migrans, although the usual associated pyrexia and low blood pressure seem to be absent. Dicoumarol is very useful in this rebellious complaint, and should be administered so as to keep the prothrombin time double the normal and persisted in for three to six months. The condition is as a rule not disabling, and the patient should, if possible, be ambulatory; this can be attained by supporting the legs with elastic bandages. A long holiday in a warm place is often beneficial. The disease is not usually dangerous and burns itself out in time, but rarely it may progress to a malignant thrombophilia in which the largest vessels may become involved and even arteries be blocked, with consequent cardiac damage or loss of limbs.

Quinine Test of Liver Function

Q.—*I have seen a reference to an article by Pallardo on the quinine test for liver function, for which he claimed good results. I should be grateful for details of procedure, the field of application, interpretation of results, and relative merits compared with other liver function tests.*

A.—The quinine test for liver function was described by Pallardo in 1947 (*Sem. méd.*, **54**, 721), and depends on the detection of quinine in the urine after oral administration of the drug. Quinine sulphate 0.2 to 0.25 g. is given to the fasting patient. The urine is collected at 30 minutes, two hours, and 12 hours afterwards. The three specimens of urine are tested for quinine with the Tanret reagent, which is prepared as follows. Dissolve 1.35 g. of mercuric chloride in 25 ml. of water, add to this solution 3.32 g. of potassium iodide dissolved in 25 ml. of water, then make the total solution up to 60 ml. with distilled water and add 20 ml. of glacial acetic acid to the mixture. After the Tanret reagent is added a positive reaction is indicated by the development of turbidity. Normal subjects give negative reactions under these conditions.

The test is positive in the urine from a high proportion of cases of liver damage, irrespective of the cause, although occasional negative findings are also recorded in conditions such as cirrhosis and infective hepatitis. The test may also be positive in cholecystitis and hepatic carcinomatosis, which would appear to limit its value in differential diagnosis. The author claims that it is a sensitive index of liver damage.

NOTES AND COMMENTS

Enlarged Liver after Amoebic Dysentery.—Dr. C. F. J. Cropper (Ronkswood, Worcester) writes: I should like to submit some comments on the answer to the query entitled "Enlarged Liver after Amoebic Dysentery" ("Any Questions?" August 20, p. 448). It appears to me that the writer was presented with a common, and in this case simple, problem to which he himself provided the solution by his demonstration of the regression of an enlarged liver beginning during the course of emetine injections. The history of amoebic dysentery and the response to this infallible therapeutic test can surely leave little doubt about the diagnosis. Incidentally, in general experience leucocytosis is frequently absent in amoebic hepatitis. There is no mention, either in the query or in the reply, of sigmoidoscopy. It is disturbing to find so essential a diagnostic procedure ignored in this way. If this neglect of sigmoidoscopy is widespread, innumerable cases of amoebiasis originating in both world wars are certainly being missed. (I use the word "both" advisedly, since more than one case has come to light in this hospital which has remained undiagnosed and untreated from the 1914–18 war: these have been diagnosed purely on sigmoidoscopy appearances.) Whilst in no way belittling the significance of stool tests, it needs to be stressed that only the select few with long apprenticeship can identify cysts with competence, and in any case the chronic patient so often yields negative results. Hand in hand with microscopy should go sigmoidoscopy, the technique and interpretation of which can readily be taught. This strangely neglected instrument frequently gives in a few moments a certain answer in the search for amoebiasis. Physicians handling cases potentially infected with this disease should have indelibly printed on their minds the picture of the tiny wart-like projections, aptly likened to colonies of pneumococci on blood-agar, which are the commonest lesions of chronic amoebic dysentery (*Lancet*, 1945, **2**, 460). In the tropical section of this hospital, in the first six months of this year no less than nineteen cases with negative stools but with dysenteric symptoms were revealed by the finding of these "pin-point craters." In the great majority of cases both symptoms and lesions cleared up with anti-amoebic treatment. There is, in my opinion, no answer to the problem of amoebiasis in this and many other countries except the adoption of sigmoidoscopy as a simple out-patient procedure.

Wax in the Ears.—Mr. F. K. Hayman (Sharnbrook, Bedford) writes: Your correspondent ("Any Questions?" October 1, p. 767) asks about any prophylaxis against wax in the ears. I have found that a good deal of so-called wax is composed of bits of hair, dandruff, ordinary dust, etc., bound together by soap—shaving or toilet—insufficiently rinsed off, and probably pushed in by the towel. I have often found a soapy turbidity in the water used for syringing, and have cautioned such patients not to allow soap to enter the meatus if possible, and in any case to rinse about the ears very thoroughly.

Dichloracetylene Poisoning.—Dr. C. F. Scurr (London, S.W.) writes: Your answer upon this subject ("Any Questions?" September 24, p. 717) is incomplete. Had the question been referred to an anaesthetist instead of an industrial toxicologist a more adequate answer would have been given. Dichloracetylene is a product of the decomposition of trichlorethylene with alkali under certain conditions—e.g., by soda lime in a closed-circuit anaesthetic apparatus. A detailed account of the toxic effects and necropsy findings is given by Humphrey and McClelland (*British Medical Journal*, 1944, **1**, 315) and by Carden (ibid., 1944, **1**, 319).

Correction

Dr. Sidney G. Hamilton (Woolacombe, N. Devon) writes that in his letter on "Antihistamine Drugs in General Practice" ("Points from Letters," October 1, p. 760) the words "phenacetin and codeine compound" in the seventh line from the end of the paragraph should read "pyranisamine maleate."

All communications with regard to editorial business should be addressed to The Editor, British Medical Journal, B.M.A. House, Tavistock Square, London, W.C.1. Telephone: Euston 2111. Telegrams: *Aitiology, Westcent, London.* ORIGINAL ARTICLES AND LETTERS forwarded for publication are understood to be offered to the *British Medical Journal* alone unless the contrary be stated.

Authors desiring REPRINTS should communicate with the Publishing Manager, B.M.A. House, Tavistock Square, W.C.1, on receipt of proofs. Authors overseas should indicate on MSS. if reprints are required, as proofs are not sent abroad.

ADVERTISEMENTS should be addressed to the Advertisement Manager, B.M.A. House, Tavistock Square, London, W.C.1 (hours 9 a.m. to 5 p.m.). Telephone: Euston 2111. Telegrams: *Britmedads, Westcent, London.*

MEMBERS' SUBSCRIPTIONS should be sent to the SECRETARY of the Association. Telephone: Euston 2111. Telegrams: *Medisecra, Westcent, London.*

B.M.A. Scottish Office: 7, Drumsheugh Gardens, Edinburgh.